TL0027-7 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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☐ Claim(s) : paged ..... to paged .....
☐ Drawing(s) : paged ..... to paged .....
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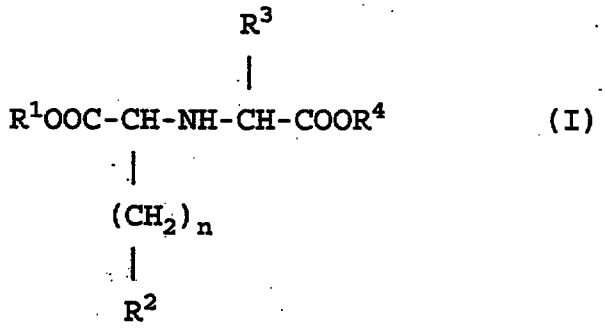
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Reductive amination of an amino acid or an amino acid derivative with an α-keto acid or an α-keto acid derivative

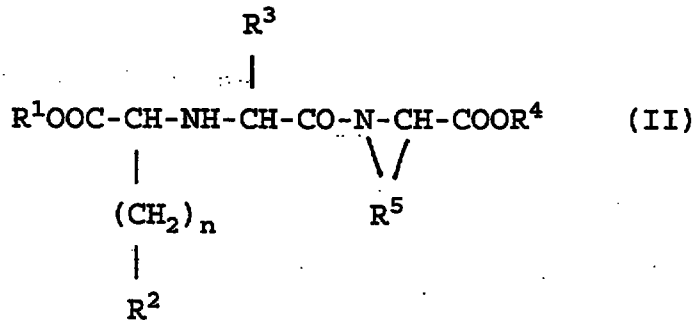
Description

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

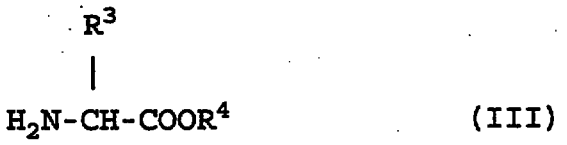
R^1 is hydrogen, methyl, ethyl or benzyl,
R^2 is hydrogen, C_1-C_4-alkyl, phenyl or phenyl-[C_1-C_4-alkyl],

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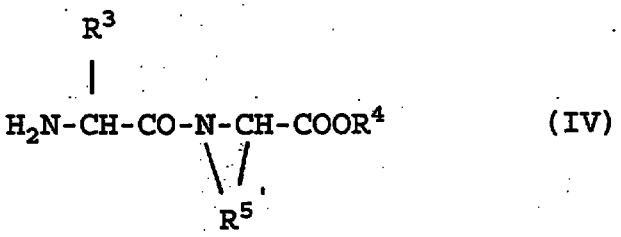
R^3 is hydrogen, heteroalkyl (*e.g.* the radical of a natural amino acid) or C_1-C_4-alkyl, benzyl, 4'-hydroxybenzyl, acylamino-[C_1-C_5]-alkyl, tert-butoxycarbonylamino-[C_1- C_5]-alkyl or benzyloxycarbonylamino-[C_1-C_5]-alkyl,
R^4 is H or an ester protecting group,
R^5 together with the atoms by which 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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* C L M S *

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.

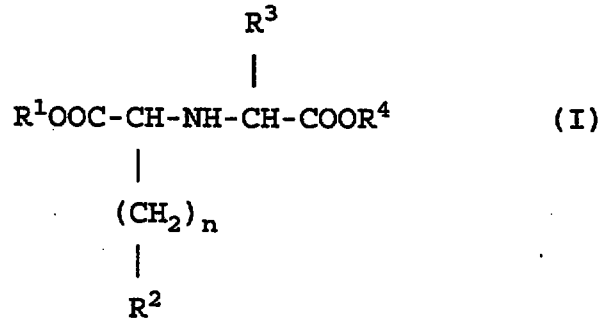
2. A reductive amination according to Claim 1, characterized in that the amino acid is an α-amino acid.

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.

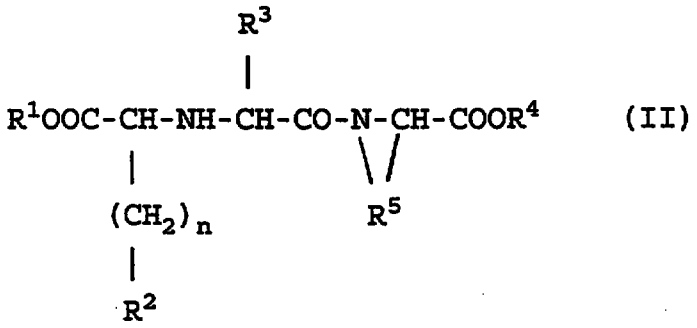
6. A reductive amination according to Claim 3 or 5, characterized in that a compound of the formula



(I)

or of the formula

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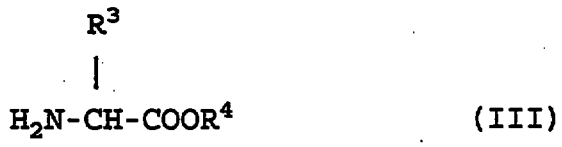


(II)

in which

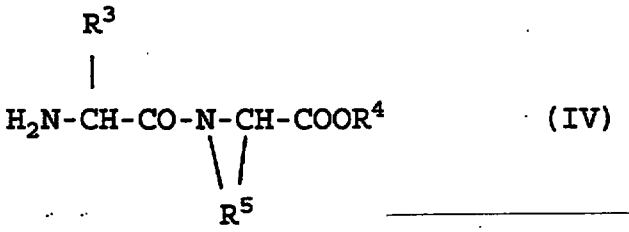
R^1 is hydrogen, methyl, ethyl or benzyl,
R^2 is hydrogen, C_1-C_4-alkyl, phenyl or phenyl-[C_1-C_4-alkyl],
R^3 is hydrogen, heteroalkyl or C_1-C_4-alkyl, benzyl, 4'-hydroxybenzyl, acylamino-[C_1-C_5]-alkyl, tert-butoxycarbonylamino-[C_1-C_5]-alkyl or benzyloxycarbonylamino- [C_1-C_5]-alkyl,
R^4 is H 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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Abstract

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

2.1. N-Substituted α-amino acids or dipeptides are valuable intermediates for the preparation of inhibitors of angiotension converting enzyme (ACE), examples of representatives being enalapril and ramipril. These compounds can be prepared by the hydrogenolytic reaction of a primary amine with a ketone, but the known processes are difficult to reproduce and generally still contain considerable amounts of by-products. The novel process makes it possible to obtain good yields and less by-products without introducing high additional costs.

2.2. According to the invention, the hydrogenolysis reaction is carried out with the addition of an organic or inorganic base, basic aluminium oxide being the preferred inorganic base. The formation of one diastereoisomer is favoured by the use of chiral organic bases.

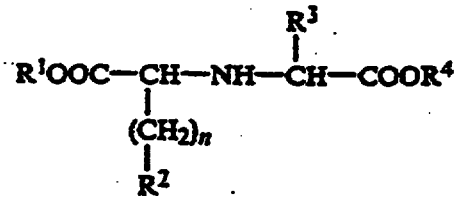
2.3. ACE, blood pressure regulators.

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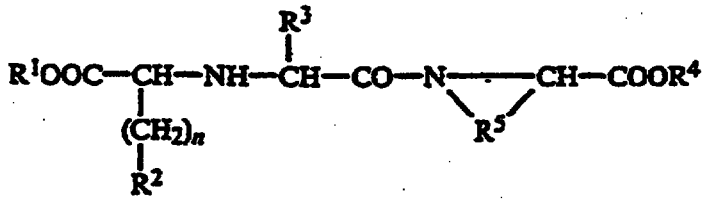
REDUCTIVE AMINATION OF AN AMINO ACID OR OF AN AMINO ACID DERIVATIVE WITH AN α-KETO ACID OR AN α-KETO ACID DERIVATIVE

The present invention relates to the reductive amination of an amino acid or of 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 hydrogenation agent, as well as, optionally, with the removal of water. More particularly, the invention relates to such a method for producing compounds of the formula(I):



(I)

or of the formula II:



(II)

in which

R^1 signifies hydrogen, methyl-, ethyl- or benzyl, R^2 signifies hydrogen, C_1–C_4-alkyl, phenyl-or phenyl-(C_1–C_4 alkyl), R^3 signifies hydrogen, heteroalkyl-(e.g. group of a natural amino acid) or C_1–C_4-alkyl, benzyl-, 4'-hydroxybenzyl-, acylamino- (C_1–C_5) -alkyl-, tert. butyloxycarbonylamino-(C_1–C_5) -alkyl-, benzyloxycarbonylamino- (C_1–C_5) -alkyl-, R^4 signifies H or an ester protective group, R^5 together with the atoms carrying it signifies a heterocyclic mono- or bicyclic ring system with 5 to 10 ring members

and

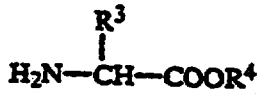
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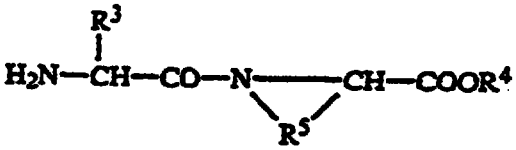
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n signifies 0, 1 or 2, by means of hydrogenolytic conversion of a compound of the formula III



(III)

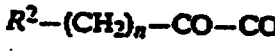
in which R^3 and R^4 have one of the meanings already indicated, in the case of preparation a compound of formula I, or through the hydrogenolytic conversion of a compound of the formula IV



(IV)

in which R^3 to R^5 have one of the meanings already indicated, in the case of preparation of compounds of formula II.

The hydrolyric conversion is carried out, in both cases, with a compound of formula V



(V),

in which R^1, R^2 and n have one of the meanings already indicated, in the presence of an inert solvent, a hydrogenation catalyst, a hydrogenation agent and with optional removal of water.

The general terms such as "alkyl", "acyl", "aromatic", in the R groups also include such groups with typical substituents, such as 4-(trifluoroacetylamino)-butyl for R^3.

BACKGROUND OF THE INVENTION

N-substituted (α-amino acids (such as in formula I) and dipeptides (such as in formula II) containing them are valuable intermediate products for the production of inhibitors of the angiotensin converting enzyme (ACE) which are highly interesting as regulators of blood pressure. A few such N-substituted dimeprides are already commercially available as medicines or are in the registration stage, e.g. enalapril (N-[(S)-1-ethoxycarbonyl-3-phenylpropyl]-L-alanyl-L-proline), lisinopril (N-[(S) -1-carboxy-3-phenylpropyl]-L-lysyl-L-pro-

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line) or ramipril (2-[N-[(S)-1-ethoxycarbonyl-3-phenyl-propyl]-L-alanyl]-(1S, 3S, 5S)-2-azabicyclo[3,3,0]-octane-3-carboxylic acid).

Such a method is described in J. Org. Chem. 1988, 53, pp. 836–844 for the production of compounds of formula II. Absolute ethanol serves as inert solvent, a molecular sieve for the removal of water and Raney nickel as hydrogenation catalyst. The products produced thereby are obtained in a 42–80 % yield according to the literature. However, these yields can be difficult to reproduce and, in addition, considerable amounts of byproducts usually remain in the products. This makes it difficult to purify them to pharmaceutically useful products.

A reductive amination of an amino acid ester with pyruvic acid is described in J. Med. Chem 28 (1985), pp. 1596–1602. The amino acid ester is used as hydrochloride. A small amount of NaOH is dissolved in the solvent, which liberates the amine from the amino acid ester hydrochloride and for the partial neutralization of the pyruvic acid. On the whole, there is an excess of acid in the reaction mixture, because of the pyruvic acid.

U.S. Pat. No. 4,474,692, especially examples 2, 7–14 and 21, teaches reductive aminations of dipeptides with α-keto acids. A buffer of sodium acetate and acetic acid is contained in the reaction mixture. The acetic acid is present the buffer in approximately double the molar excess.

SUMMARY OF THE INVENTION

The object of the present invention is to provide a modification of the known method which increases yields and which minimizes byproducts and which also minimizes expense. A further object is to provide such a method which enables the making of diastereoisomers, if desired.

These and other objects are achieved in a method in which the hydrogenolytic conversion is carried out in the presence of excess of an organic or inorganic base.

An excess of base is provided if the adducts used have been adjusted to their isoelectric point and then one or several compounds are still present in the system which decrease, in water, the hydrogen ion concentration of the water and/or which take up protons from water molecules, thus bringing about the formation of hydroxide ions, or, insofar as the pK value of the adducts used

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(their isoelectric point) is below pH 7, raising the pH in water above the pK value of the adducts.

The pH of the system (relative to the aqueous concentration) is preferably approximately at least 5.0 and advantageously approximately at least 6.0. Values of 6.2 and higher are especially suitable, with 11 and especially 10 being advantageous upper values.

This excess surprisingly clearly increases the chemical yield of the conversion even though the first step of the reaction, the imine formation (Roberts, J.D.; Caserio, M.C.; Basic Principles of Organic Chemistry, 2nd edition, W.A. Benjamin Inc., Philippines, 1977, pp. 697, 1154), is catalyzed by acid. Weak bases, such as organic bases such as mono-, di- or trierhanoi amine, trimethylamine, triethylamine, tripropylamine, tributylamine or N-methylmorpholine are especially suitable.

Suitable inorganic bases are salts of weak acids such as NaOAc, K_2CO_3, $KHCO_3$, Na_2CO_3 and, especially preferred, basic aluminum oxide.

Strong bases can also support the reaction, especially in very dilute concentration.

It is preferable if the excess base raises the (theoretical) pH of the reaction system only slightly above the pK value of the adducts. An elevation of 0.1 to 3, preferably 0.3 to 2 pH steps is customary.

The base is advantageously added in an amount of 0.01 to 5 molar equivalents, preferably from 0.05 to 2 molar equivalents relative to the amount of the compound of formula III or the compound of formula IV used. When using organic bases, hypostoichiometric amounts, especially 0.08–0.6 molar equivalents are particularly preferred.

The amino function of the amino acids or amino acid derivatives used must be present during the reaction at least partially in the form of a primary amine; this is also the case in the method of the present invention if this compound is used as an inner salt or otherwise as a salt, e.g. as hydrochloride.

The amino acid derivative is preferably an ester of an amino acid or an amide of the acid function; the amidic bonding preferably takes place with an additional amino acid or amino acid derivative so that the amino acid derivative is a di- or oligopeptide. On the whole, α-amino acids or their derivatives are preferred.

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Compounds of formula V are particularly preferred in the form of α-keto acids or their derivatives, with pyruvic acid as the simplest representative.

The reaction usually requires the removal of the water produced. This can be achieved through the use of a water binding agent, preferably inert or basic. Suitable water binding agents are e.g. molecular sieves and aluminum oxides. The removal of water is particularly advantageous in the reaction of the keto group with the amine to the imine and is indicated in particular when using α-keto esters. Otherwise the reduction of the keto function as a side reaction could also possibly take place to a greater extent.

The addition of the organic base frequently makes it possible to distinctly reduce the amount of molecular sieve added as water binding agent and the addition of a basic aluminum oxide can render the molecular sieve quite superfluous because it functions itself simultaneously as a water binding agent. This reduces cost and minimizes by-products.

If an inorganic base, e.g. a basic aluminum oxide is used as an additive, this advantageously is used in an amount of 50 g/mole to 500 g/mole, relative to the amount of the compound of formula III or IV used, if the reaction water formed is to be bound with this base at the same time, otherwise in amounts of 2 to 400 g/mole.

The solvents used should preferably be anhydrous. Suitable inert solvents for the method of the invention are alcohols such as methanol, ethanol, propanol or butanol; ethers such as ethylene glycol dimethylether, diethylene glycol dimethylether or tetrahydrofuran; and carboxylic acid dialkylamides such as dimethylformamide or dimethylacetamide. Mixtures of such solvents can be used. It is advantageous if at least one protic solvent is used.

The hydrogenation catalysts and hydrogenation agents are preferably Raney nickel, palladium or palladium on activated carbon and platinum or platinum on activated carbon as well as H_2. If no stereoselectivity is desired, hydrides can also be used as hydrogenation catalysts and hydrogenation agents. Raney nickel is especially preferred since diastereoselectivity is best when it is used.

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Among the diastereomers produced during the reaction, the S-configured product is usually preferred. The diastereoselectivity of the conversion required for the preferred production of the enantiomer can be increased even more, in many instances, if a chiral organic base is used. Such bases are, e.g., L- or D-prolinol, L- or D-valinol, (−)- or (+)-ephedrine and (−)- or (+)-norephedrine, which often increase the formation of an enantiomer, depending on the compounds used.

In the production of compounds of formula I, the naturally occurring α-amino acids or their optical antipodes, optionally in protected form, are preferred as compounds of formula III. Examples include are alanine, valine, methionine, cysteine, serine, tryptophane, asparagine, glutamine, aspartic acid, glutamic acid, phenylalanine, tyrosine, leucine, isoleucine or glycine and their esters, e.g. the benzyl-, tert. butyl- or ethyl esters (ester protective groups). If lysine or ornithine is used as the compound of formula III, the amino group in the side claim must be protected, such as by means of a trifluoroacetyl-, carbobenzoxy- or tert. butyloxycarbonyl group.

It can be advantageous during the conversion of compounds of formula III with a compound of formula V if they are first combined and heated with the aid of a suitable water-entraining solvent, such as cyclohexane, methyl-tert. butyl ether or toluene, to separate water and are azeotropically dehydrated in this manner. The compounds of formula III as well as of formula II can optionally also be used in the form of salts, e.g. as para toluene sulfonates or hydrochlorides, if R^4 does not signify H. In order to convert the salts into their free amines, the base should be present in a molar ratio of up to 100 mole % in the azeotropic dehydration. Weak bases such as N-methylmorpholine are preferred for this purpose. Care must be taken, in this procedure, that the formation of lactones or dimerization products of compound V is avoided, and high temperatures (especially above 100° C.) should also be avoided. If necessary, the solvent is subsequently changed and hydrogenolytically converted, that is, the base and the hydrogenation catalyst are added.

During the production of compounds of formula II, the following are preferably used as compounds of formula IV: Dipeptides from a naturally occurring α-amino acid or its antipodes, optionally protected in a possible side chain functionality, in the N-terminal position and from a cyclic (α-amino acid in the C-terminal

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position. Examples are alanyl-proline, N^{ϵ}-trifluoroacetyl-lysyl-proline, N^{ϵ}-carbobenzoxy-lysyl-proline, N^{ϵ}-tert.butyloxycarbonyl-lysyl-proline, N^{δ}-trifluoroacetyl-ornithyl-proline, N^{δ}-carbobenzoxy-ornithyl-proline or N^{δ}-tert.butyloxycarbonyl-ornithyl-proline.

2-oxo-4-phenyl-butyric acid ethyl ester is preferably used as the compound of formula V. The compounds of formula V are advantageously used in a 0.05 to simple [onefold] molar excess over the compound of formula III or IV.

In the practical execution of the method of the invention, a compound of formula V and a compound of formula III or IV are dissolved or suspended in the inert solvent. After the possible addition of a molecular sieve or aluminum oxide as a water binding agent, the organic or inorganic base (insofar as still necessary) is added. The reaction mixture is then advantageously preagitated for a time sufficient to bind any water still contained in it to the molecular sieve or to the basic aluminum oxide. The Schiff base also forms, during which time the water produced is likewise bound. After this preactivation, the previously dehydrated hydrogenation catalyst is added and the hydrogenolytic conversion is carried out under an atmosphere of hydrogen. An excess hydrogen pressure between 1 and 8 bars is especially preferred.

The method of the invention is especially advantageous in the case of reductive aminations which otherwise give no yields or only slight yields when catalyzed by acid (with an excess of acid) or at the isoelectric point (pK) of the adducts.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The following examples illustrate the method of the invention in more detail:

EXAMPLE 1:

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

50 mmoles (9.3 g) Ala-Pro were suspended in 100 ml ethanol, mixed with 10 moles (1 g) triethylamine, 75

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mmoles (15.5 g) 2-oxo-4-phenyl-butyric acid ethyl ester and 18 g molecular sieve 3 A and agitated for 2 hours under anhydrous conditions. One teaspoon of dehydrated Raney nickel and 15 g molecular sieve 3 A were now added, briefly reacted and subsequently hydrogenated for 22 hours under an atmosphere of 4 bars of H_2. The reaction mixture was filtered and evaporated to concentrate it to a small volume. Conversion (according to HPLC) relative to Ala-Pro used: 95.6%, product yield (according to HPLC): 95%. The residue was taken up in 250 ml ethanol and adjusted to pH 4.25 with conc. HCl (an aliquot was removed for this purpose, diluted with water and the pH adjusted, then the entire amount of HCl required was calculated). The solution was evaporated to low bulk under reduced pressure at 40° C. to 50 g, filtered with Celite and diluted to 100 ml total volume with ethyl acetate. 5.2 g maleic acid dissolved in ethyl acetate+ethanol were added and the mixture was seeded with enalapril maleate. The crystallizate formed was separated off and dried.

Yield: 20.9 g=85% of theory>99% SSS diastereomer, melting point: 145–146° C., $[\alpha]_D^{25}$: 42° (c=1 in MeOH).

Comparative Example

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

50 moles (9.3 g) Ala-Pro were suspended in 100 ml ethanol, combined with 75 moles (15.5 g) 2-oxo-4-phenyl-butyric acid ethyl ester and 18 g molecular sieve 3 A and agitated for 2 hours under anhydrous conditions. One teaspoon of dehydrated Raney nickel and 15 g molecular sieve 3 A were now added, briefly reacted and subsequently hydrogenated for 22 hours under an atmosphere of 4 bars of H_2. The reaction mixture was filtered and evaporated to concentrate it to a small volume. Conversion (according to HPLC) relative to Ala-Pro used: 76.7%, product yield (according to HPLC): 35%. The residue was taken up is 250 ml ethanol and adjusted to pH 4.25 with conc. HCl (an aliquot was removed for this purpose, diluted with water and the pH was adjusted, then the entire amount was calculated). The solution was evaporated to low bulk under

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reduced pressure at 40° C. to 50 g, filtered by Celite and diluted to 100 ml total volume with ethyl acetate. 5.2 g maleic acid dissolved in ethyl acetate+ethanol were added and seeded with enalapril maleate. The crystallizate formed was separated off and dried.

Yield: 7.4 g=30% of theory,>99% SSS diastereomer, melting point: 145–146C, $[\alpha]_D^{25}$: 42° (c=1 in MeOH).

Example 2:

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

The same procedure was used as in Example 1; however, instead of triethylamine, 0.8 molar equivalent of ethanolamine were added as the base. Conversion (according to HPLC) relative to Ala-Pro: 85%, product yield (according to HPLC): 85%, diastereoisomer ratio before crystallization: SSS:RSS isomer=88.12

Example 3:

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

150 mmoles H-N^{ϵ}-TFA-Lys-Pro-OH (50.9 g) were taken up in 120 ml n-butanol and approximately 50 ml n-butanol distilled off under vacuum. The solution was diluted with 500 ml ethanol. 22.5 g molecular sieve 3 A, 34 g 2-oxo-4-phenyl butyric acid ethyl ester and 30 mmoles triethylamine (4.2 ml) are added and the mixture agitated 2 hours under anhydrous conditions. Three teaspoons dehydrated Raney nickel were now added and the mixture was agitated for 4 hours at under an atmosphere of 4 bars of H_2. After this time, the pressure was released, another 12.4 g 2-oxo-4-phenyl butyric acid ethyl ester was added and the mixture was reagitated for 2 hours. Then a pressure of 4 bars of hydrogen was applied and the mixture was hydrogenated a further 4 hours at this pressure. The catalyst was separated off (it can be directly reused) and the solution was evaporated to a small volume. Conversion (according to HPLC) relative to N^{ϵ}-TFA-Lys-Pro: approximately 95%, product yield (according to HPLC): 90%, diastereomer ratio: SSS:RSS-isomer=95.5. The residue was suspended in 450 ml water and 450 ml 1,1,1-trichloroethane at 5° C., the pH was adjusted to 9.6 in the

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aqueous phase with 50% NaOH and the phases were thoroughly mixed. The organic phase was separated off and the aqueous product phase was post-extracted with 100 ml 1,1,1-trichloroethane. The pH of 4.6 was now adjusted to 5 in the aqueous phase and this phase was extracted twice with 400 ml 1,1,1-trichloroethane. The organic phase was evaporated to low volume and taken up in 250 ml methyl-tert.butyl ether. The solution was cooled down to 0° C. and seeded. Yield: 48 g (60% of theory), SSS diastereomer content: >99%, $[\alpha]_D^{20}$:—25.5° [(c=1 in MeOH/ ·1N HCl (1:1)].

EXAMPLE 4

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

The same procedure was used as in Example 4; however, instead of triethylamine, 0.2 molecular equivalent of tributylamine were added as the base. Conversion (according to HPLC) relative to N^{ϵ}-TFA-Lys-Pro: 85%, product yield (according to HPLC): 75%, diastereomer ratio before crystallization: SSS:RSS diastereomer=96.4:3.6.

EXAMPLE 5

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

The same procedure was used as in Example 4; however, instead of triethylamine, 0.8 molar equivalent ethanol amine were added as base. Conversion (according to HPLC) relative to N^{ϵ}-TFA-Lys-Pro: 75%, product yield (according to HPLC): 65%, diastereomer ratio before crystallization: SSS:RSS diastereomer=93:7.

EXAMPLE 6

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

The same procedure was used as in Example 4; however, instead of triethylamine, 0.2 molar equivalent L-prolinol were added as base.

Conversion (HPLC) relative to N^{ϵ}-TFA-Lys-Pro: 85%, product yield (HPLC): 65%, diastereomer ratio before crystallization: SSS:RSS diastereomer=95:5.

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EXAMPLE 7

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

The same procedure was used as in Example 4; however, instead of triethylamine, 0.2 molar equivalent (1R,2S)-(−)-ephedrine were added as base. Conversion (according to HPLC) relative to $^{\epsilon}$-TFA-Lys-Pro: 84%, product yield (according to HPLC): 70%, diastereomer ratio before crystallization: SSS:RSS diastereomer=96.7:3.3.

EXAMPLE 8

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

The same procedure was used as in Example 4; however, 0.1 molar equivalent triethylamine were added as base. Conversion (according to HPLC) relative to N^{ϵ}-TFA-Lys-Pro: 75%, product yield (HPLC): 60%, diastereomer ratio before crystallization: SSS:RSS diastereomer=97.7:2.3.

EXAMPLE 9

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

The same procedure was used as in Example 4; however, instead of molecular sieve and base, 25 g basic activated aluminum oxide were added. Conversion (according to HPLC) relative to N^{ϵ}-TFA-Lys-Pro: 95%, product yield (HPLC): 80%, diastereomer ratio before crystallization: SSS:RSS diastereomer=95.5:4.5.

EXAMPLE 10

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

The same procedure was used as in Example 4; however, instead of Raney nickel, palladium 1% on carbon was used as catalyst. Conversion (according to HPLC) relative to N^{ϵ}-TFA-Lys-Pro: 90%, product yield (according to HPLC): 80%, diastereomer ratio before crystallization: SSS:RSS diastereomer=62:38.

EXAMPLE 11

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

250 mmoles L-alanine benzyl ester p-toluene sulfonic

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acid salt (88 g) and 312.5 mmoles 2-oxo-4-phenyl butyric acid ethyl ester (65 g) were suspended in 500 ml cyclohexane. After the addition of 250 mmoles N-methylmorpholine (25.3 g), water was removed by azeotropic distillation until the end of the reaction. After the mixture had cooled, it was filtered to remove salts, evaporated to low volume and taken up in 400 ml anhydrous methanol. After the addition of 25 mmoles N-methylmorpholine (1 g) and 3 teaspoons anhydrous Raney nickel, the mixture was hydrogenated at 4 bars excess hydrogen pressure and room temperature until the adsorption of hydrogen stopped. The reaction mixture was filtered from the catalyst, post-washed with warm methanol and evaporated to low volume. The residue was partitioned at 5° C. and pH 9.6 between water and 1,1,1-trichloroethane. The aqueous phase was subsequently extracted at pH 3 and 5° C. with 1,1,1-trichloroethane and the organic phase evaporated to low volume. The residue was crystallized from ethanol or acetone while cold.

Yield: 1st fraction: 35 g; 2nd fraction: 12 g

Melting point: 143–145° C.

What is claimed is:

1. In a reductive amination of an α-keto-compound selected from the group consisting of α-keto acids and α-keto acid derivatives of the Formula (V)

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

in which

R^1 signifies hydrogen, methyl, ethyl or benzyl,

R^2 signifies hydrogen, C_1-C_4-alkyl, phenyl or phenyl(C_1-C_4-alkyl), and

n signifies 0, 1 or 2,

with an amino-compound of the Formula (III)

$$H_2N-\underset{\displaystyle R^3}{\underset{|}{C}}H-COOR^4 \qquad (III)$$

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acid salt (88 g) and 312.5 mmoles 2-oxo-4-phenyl butyric acid ethyl ester (65 g) were suspended in 500 ml cyclohexane. After the addition of 250 mmoles N-methylmorpholine (25.3 g), water was removed by azeotropic distillation until the end of the reaction. After the mixture had cooled, it was filtered to remove salts, evaporated to low volume and taken up in 400 ml anhydrous methanol. After the addition of 25 mmoles N-methylmorpholine (1 g) and 3 teaspoons anhydrous Raney nickel, the mixture was hydrogenated at 4 bars excess hydrogen pressure and room temperature until the adsorption of hydrogen stopped. The reaction mixture was filtered from the catalyst, post-washed with warm methanol and evaporated to low volume. The residue was partitioned at 5° C. and pH 9.6 between water and 1,1,1-trichloroethane. The aqueous phase was subsequently extracted at pH 3 and 5° C. with 1,1,1-trichloroethane and the organic phase evaporated to low volume. The residue was crystallized from ethanol or acetone while cold.

Yield: 1st fraction: 35 g; 2nd fraction: 12 g

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What is claimed is:

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

in which

R^1 signifies hydrogen, methyl, ethyl or benzyl,

R^2 signifies hydrogen, C_1-C_4-alkyl, phenyl or phenyl(C_1-C_4-alkyl), and

n signifies 0, 1 or 2,

with an amino-compound of the Formula (III)



$$H_2N-\underset{\displaystyle R^3}{\underset{|}{CH}}-COOR^4 \qquad (III)$$

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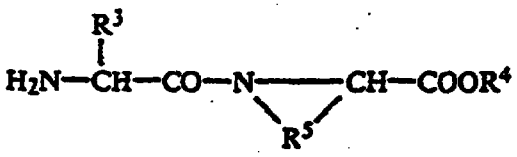
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in which

R_3 signifies hydrogen, heteroalkyl-, or C_1–C_4 alkyl, benzyl-, 4'-hydroxybenzyl, acrylamino-(C_1–C_5)-alkyl, tert.butyloxycarbonylamino-(C_1–C_5)-alkyl, benzyloxycarbonylamino-(C_1–C_5)-alkyl-, and

R^4 signifies H or an ester protective group, or Formula (IV)



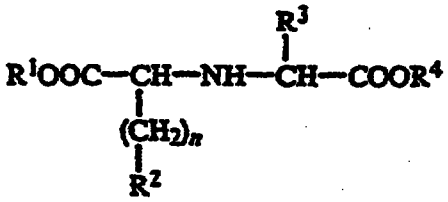
(IV)

in which

R^3 and R^4 have one of the meanings already indicated and

R^5 together with the atoms carrying it signifies a heterocyclic mono- or bicyclic ring system with 5 to 10 members

in an inert solvent, and in the presence of a hydrogenation catalyst and a hydrogenation agent, both acting together to reduce a double bond in an intermediate formed by condensation of said keto-compound with said amino-compound to a single bond by incorporating hydrogen, so as to form a C-N bond between the C-atom of the keto-group of said keto-compound and the N-atom of the amino group of said amino-compound yielding a compound for Formula (I):



(I)

in which

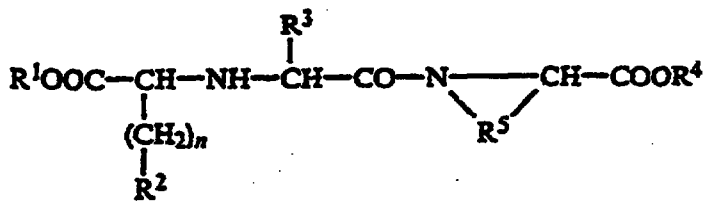
R^1 to R^4 and n have one of the meanings already indicated in the case that the compound of Formula (V) is reacted by means of hydrogenolytic conversion with a compound of Formula (III), or a compound of Formula (II):

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(II)

in which R^1 to R^5 and n have one of the meanings already indicated in the case that the compound of Formula (V) is reacted by means of hydrogenolytic conversion with a compound of Formula (IV), as well as optionally removing water;

the improvement in which the reductive amination is carried out in the presence of an excess of base, an excess of base being provided if the adducts used have been adjusted to their isoelectric point and then at least one compound is still present in the system which decreases, in water, the hydrogen ion concentration of the water and/or which takes up protons from water molecules, or, if the pK value of the adducts used is below pH 7, which raises the pH of the water above the pK value of the adducts.

2. A method according to claim 1 in which mono-, di- or triethanol amine, trimethylamine, triethylamine, tripropylamine, tributylamine, N-methylmorpholine, L-or D-prolinol, L- or D-valinol, (—)- or (+)-ephedrine, (—)- or (+)-norephedrine are used as an organic base.

3. The method according to claim 1 in which K_2CO_3, Na_2CO_3, $KHCO_3$, NaOAc, $NaHCO_3$ or basic aluminum oxide are used as inorganic base.

4. The method according to claim 1 in which the base is added in an amount of 0.01 to 5 equivalents relative to the compound of formula III or IV used.

5. The method according to claim 4 in which the base is added in an amount of 0.05–2 equivalents relative to the compound of formula III or IV used.

6. The method according to claim 4 in which the base is an organic base and it is added in an amount of 0.08–0.6 molar equivalents relative to the compound of formula III or IV used.

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7. The method according to claim 1 in which the basic aluminum oxide is added in an amount of 2 g/mole to 400 g/mole relative to the compound of formula III or IV added.

8. The method according to claim 1 in which basic aluminum oxide is added as a water binding agent for the removal of water.

9. The method according to claim 8 in which the basic aluminum oxide is added in an amount of 50 g/mole to 500 g/mole relative to the compound of formula III or IV added.

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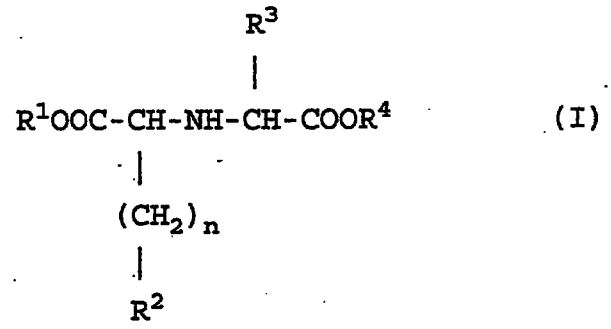
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☑ Claim(s) : paged 16.. to paged 11.
☐ Drawing(s) : paged ..... to paged .....
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Reductive amination of an amino acid or an amino acid derivative with an α-keto acid or an α-keto acid derivative

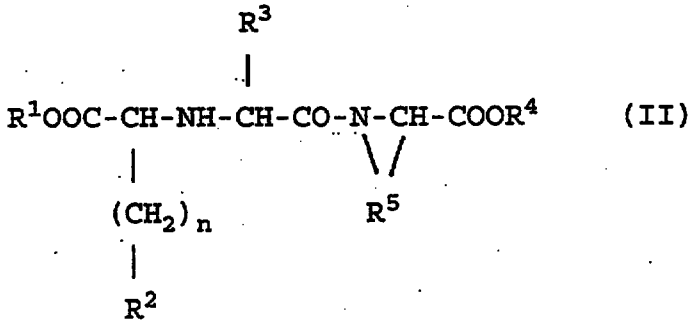
Description

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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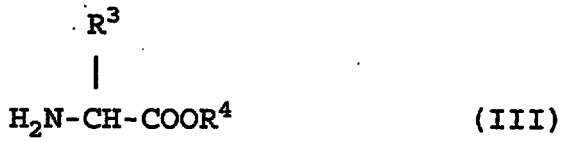


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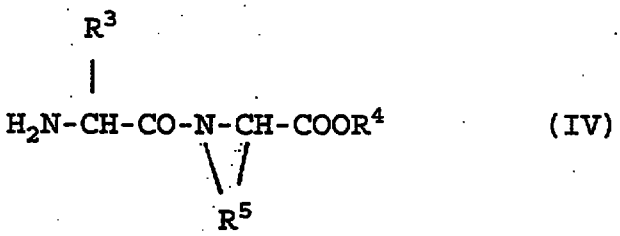
R^3 is hydrogen, heteroalkyl (*e.g.* the radical of a natural amino acid) or C_1-C_4-alkyl, benzyl, 4'-hydroxybenzyl, acylamino-[C_1-C_5]-alkyl, tert-butoxycarbonylamino-[C_1- C_5]-alkyl or benzyloxycarbonylamino-[C_1-C_5]-alkyl,
R^4 is H or an ester protecting group,
R^5 together with the atoms by which 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/

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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.

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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.

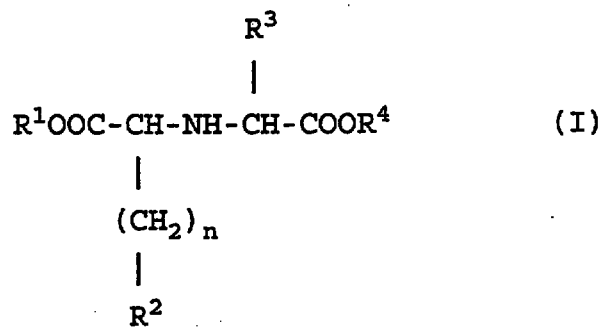
2. A reductive amination according to Claim 1, characterized in that the amino acid is an α-amino acid.

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)

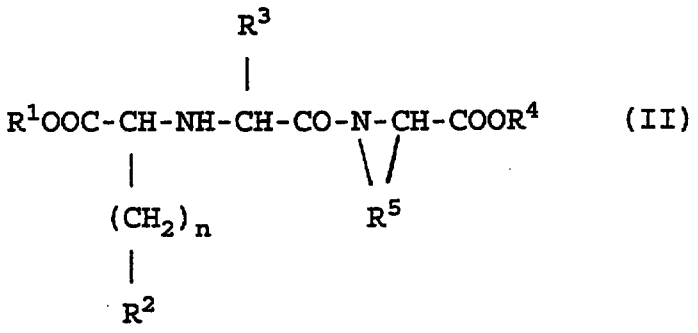
or of the formula

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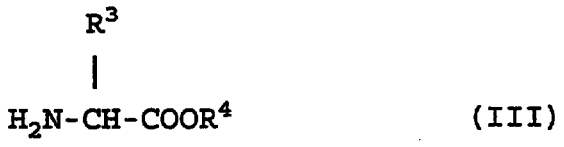


(II)

in which

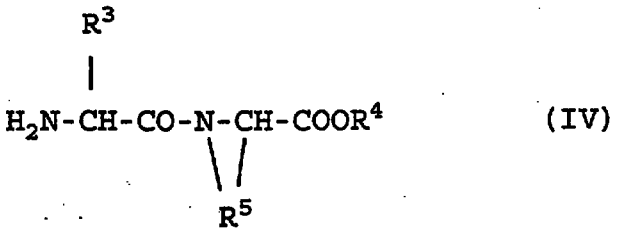
R^1 is hydrogen, methyl, ethyl or benzyl,
R^2 is hydrogen, C_1-C_4-alkyl, phenyl or phenyl-[C_1-C_4-alkyl],
R^3 is hydrogen, heteroalkyl or C_1-C_4-alkyl, benzyl, 4'-hydroxybenzyl, acylamino-[C_1-C_5]-alkyl, tert-butoxycarbonylamino-[C_1-C_5]-alkyl or benzyloxycarbonylamino- [C_1-C_5]-alkyl,
R^4 is H 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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Abstract

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

2.1. N-Substituted α-amino acids or dipeptides are valuable intermediates for the preparation of inhibitors of angiotension converting enzyme (ACE), examples of representatives being enalapril and ramipril. These compounds can be prepared by the hydrogenolytic reaction of a primary amine with a ketone, but the known processes are difficult to reproduce and generally still contain considerable amounts of by-products. The novel process makes it possible to obtain good yields and less by-products without introducing high additional costs.

2.2. According to the invention, the hydrogenolysis reaction is carried out with the addition of an organic or inorganic base, basic aluminium oxide being the preferred inorganic base. The formation of one diastereoisomer is favoured by the use of chiral organic bases.

2.3. ACE, blood pressure regulators.

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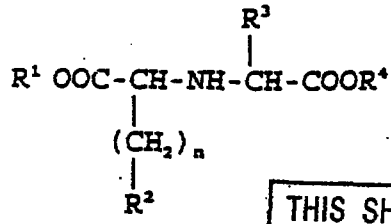
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REDUCTIVE AMINATION OF AN AMINO ACID OR AN AMINO ACID DERIVATIVE WITH AN ALPHA-KETO ACID OR AN ALPHA-KETO DERIVATIVE

Description

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



(I)

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☑ Claim(s) : paged ..16.. to paged ..19..
☐ Drawing(s) : paged ..... to paged .....
☐ Abstract : paged ..... to paged .....
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wherein

R^1 signifies hydrogen, methyl, ethyl or benzyl,

R^2 signifies C_1-C_4-alkyl, phenyl or phenyl-[C_1-C_4-alkyl],

R^3 signifies hydrogen, heteroalkyl or C_1-C_4-alkyl, benzyl, 4'-hydroxybenzyl, acylamino-[C_1-C_5]-alkyl, tert.-butyloxy-carbonylamino-[C_1-C_5]-alkyl, benzyloxycarbonylamino-[C_1-C_5]-alkyl,

R^4 signifies H or an ester protecting group,

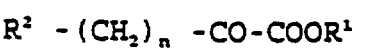
n is 0, 1 or 2,

by hydrogenolytic conversion of a compound of the formula



(III),

wherein R^3 and R^4 have one of the meanings already given, with a compound of the formula

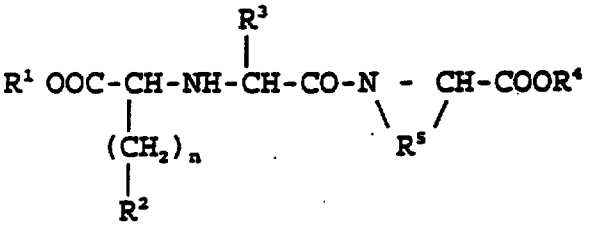


(V),

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wherein R^1, R^2 and n have one of the meanings already given,

or that compounds of the formula

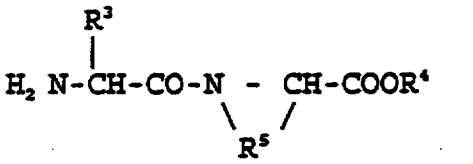


(II),

wherein R^1, R^2, R^3, R^4 and n have the meanings given above,

R^5 together with the atoms carrying it signifies a heterocyclic monocyclic or bicyclic ring system having 5 to 10 ring members,

are obtained by hydrogenolytic conversion of a compound of the formula



(IV),

wherein R^3 to R^5 have one of the meanings already given, with a compound of the formula

$R^2 - (CH_2)_n - CO - COOR^1$ (V),

wherein R^1, R^2 and n have one of the meanings already given, in the presence of an inert solvent, a hydrogenating catalyst, a hydrogenating agent and optionally with the removal of water. In principle "alkyl", "acyl", "aromatic" et cetera in the radicals R also include corresponding radicals having typical substituents, for example, 4-(trifluoroacetylamino)butyl for R^3.

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N-substituted α-amino acids (such as I) and dipeptides containing these (such as II) are valuable intermediate products for the preparation of inhibitors of the Angiotensin Converting Enzymes (ACE), which are of great interest as blood pressure regulators. Several of these N-substituted dipeptides are already available on the market as medicines or are at the stage of being licenced, for example, 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]-octan-3-carboxylic acid).

A method of this kind is described in J. Org. Chem. 1988, 53, 836-844 for the preparation of compounds of the formula (II). Absolute ethanol is used as inert solvent, a molecular sieve is used for the removal of water and the hydrogenating catalyst used is Raney nickel. The products formed here are, according to the literature, obtained in a 42% to 80% yield. These yields can however be difficult to reproduce; moreover in most cases the products still contain considerable quantities of secondary products, which render difficult purification into pharmaceutically usable products.

A reductive amination of an amino acid ester using pyruvic acid is described in J. Med. Chem. 28 (1985), 1596-1602. The amino acid ester is used in the form of a hydrochloride. A small quantity of NaOH is dissolved in the solvent; this serves to release the amine from the amino acid ester hydrochloride and to partly neutralise the pyruvic acid. Overall there is an excess of acid in the reaction mixture, caused by the pyruvic acid.

Other reductive aminations of dipeptides using α-keto acids are known from US-PS 4,474,692, in particular Examples 2, 7 to 14 and 21. The reaction mixture contains a buffer of

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sodium acetate and acetic acid, in which the acetic acid is present in an approximately twice molar excess.

The object of the invention is a modification of the known method with a view to obtaining high yields accompanied by fewer secondary products, without any high additional costs resulting. Moreover the reaction - if so desired - is to be controllable with regard to the formation of diastereoisomers.

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

There is an excess of base in respect of the overall system when throughout the entire reaction the molar ratio of base functions and acid functions is greater than 1.

Surprisingly, the chemical yield of the reaction is distinctly increased by this excess, although the first step of the reaction, the formation of imine (Roberts, J. D., Caserio, M. C.: Basic Principles of Organic Chemistry, 2nd Ed., W. A. Benjamin Inc., Philippines, 1977, pages 697, 1154), is catalysed by acids. Weak bases are particularly suitable, for example, organic bases such as mono-, di- or triethanolamine, trimethylamine, triethylamine, tripropylamine, tributylamine or N-methylmorpholine.

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

Strong bases, particularly in very dilute concentration, can also promote the reaction.

The base is suitably added in a quantity of from 0.01 to 5 mole equivalents, preferably of from 0.05 to 2 mole equivalents, in each case referred to the compound used having the formulae (III) or (IV). When organic bases are used, substoichiometric quantities, in particular of from 0.08 to 0.6 mole equivalents, are particularly preferred.

The amino function of the amino acids or amino acid derivatives used must be at least partly in the form of a primary amine during the reaction. This is also provided by the method according to the invention, when these compounds are used as an internal salt or else as a salt, for example, as hydrochloride.

The amino acid derivative is preferably an ester of the amino acid or an amide of the acid function, with the amide bonding preferably taking place with another amino acid or amino acid derivative, so that the amino acid derivative is a dipeptide or oligopeptide. On the whole the use of α-amino acids or the derivatives thereof is preferred.

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

In most cases the reaction requires the removal of the water formed; the water-binding agent employed is preferably inert or basic.

Examples of suitable water-binding agents are molecular sieves and aluminium oxides. The removal of water is especially advantageous in the reaction of the keto group with the amine to form imine and is advisable above all when α-keto esters are used, as otherwise it is possible that the reduction of the keto function as a secondary reaction may take place more vigorously.

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The addition of the organic base often makes it possible to significantly decrease the quantity of molecular sieve used as water-binding agent. The addition of a basic aluminium oxide may possibly render the molecular sieve wholly dispensable, because the aluminium oxide itself simultaneously serves as a water-binding agent. Apart from a cost saving, this results primarily in fewer waste products.

If an inorganic base, for example, a basic aluminium oxide, is used as an additive, then it is suitably added in a quantity of from 2 g/mol to 400 g/mol, referred to the compound used having the formula (III) or (IV), or, if the water of reaction formed is simultaneously to be bound by the said base, in quantities of from 50 to 500 g/mol.

The solvents used should preferably be anhydrous. Suitable inert solvents for the method 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 dialkyl amides, such as dimethylformamide or dimethylacetamide. Mixtures of these solvents may also be used. It is advantageous to use at least one protonic solvent.

The hydrogenating catalysts and hydrogenating agents used are preferably Raney nickel, palladium or palladium on activated carbon and platinum or platinum on activated carbon, as well as H_2. When stereoselectivity is not required, hydrides may also be used as hydrogenating catalysts and hydrogenating agents. Raney nickel is particularly preferred, as the diastereoselectivity is best when it is used.

Of the diastereoisomers formed during the reaction, in most cases the S-configured product is preferred. The

diastereoselectivity of the reaction required for the preferred preparation of the enantiomer can in many cases be increased still further when a chiral organic base is used. Examples of such bases are L- or D-prolinol, L- or D-valinol, (-)- or (+)-ephedrine and (-)- or (+)-norephedrine which, depending on the compounds involved, often promote the formation of an enantiomer.

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

In the reaction of compounds of the formula (III) with a compound of the formula (V) it may be advantageous if these are first mixed together and, with the aid of a suitable water-entraining solvent, for example, cyclohexane, methyl tert. butyl ether or toluene, are heated with the separation of water and thus azeotropically dehydrated. Here the compounds of the formula (III) as well as those of the formula (II) can also optionally be used in the form of salts, for example, as paratoluenesulphonates or hydrochlorides, unless R^4 signifies H. In order to convert the salts into their free amines, during the azeotropic dehydration the base should already be present in a molar ratio of up to 100 mol-%. Here the weak bases such as N-methylmorpholine are preferred. During this procedure care must be taken that the formation of lactones or

dimerisation products of the compound (V) is avoided. An elevated temperature (especially above 100°C) should correspondingly be avoided. Subsequently the solvent is optionally changed and hydrogenolytically converted, that is, the base and the hydrogenating catalyst are added.

In the preparation of compounds of the formula (II), the compounds of the formula (IV) preferably used are dipeptides consisting of a naturally occurring α-amino acid or the antipodes thereof, if necessary protected in any side chain functionality, in an N-terminal position and of a cyclic α-amino acid in a C-terminal position. Examples are alanylproline, N^{ϵ}-trifluoroacetyllysylproline, N^{ϵ}-carbobenzoxylysylproline, N^{ϵ}-tert. butyloxycarbonyllysylproline, N^{δ}-trifluoroacetylornithylproline, N^{δ}-carbobenzoxyornithylproline or N^{δ}-tert. butyloxycarbonylornithylproline.

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

In the practical carrying out of the method according to the invention, a compound of the formula (V) and a compound of the formula (III) or (IV) are dissolved or suspended in the inert solvent. After optional addition of a molecular sieve or aluminium oxide as a water-binding agent, the organic or inorganic base (if still required) is added. It is advisable then to prestir the reaction mixture for a fairly long period of time, in order to bind any water possibly still contained therein to the molecular sieve or the basic aluminium oxide. Here the Schiff's base is also formed, with the water produced likewise being bound. After this preactivation, the previously dehydrated hydrogenating catalyst is added and the hydrogenolytic conversion is carried out in an atmosphere of hydrogen. In the course of

this an excess hydrogen pressure of between 1 and 8 bar is particularly favourable.

The method according to the invention is advantageous particularly in reductive aminations which do not proceed when catalysed by acid (in an excess of acid) or do so with only small yields.

The method according to the invention is explained in more detail by the following Examples.

Example 1

N$^{\alpha}$-[(S)-1-ethoxycarbonyl-3-phenylpropyl]-L-alanyl-L-proline

50 mmol (9.3 g) of ala-pro was 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 molecular sieve 3 A were added thereto and the suspension was stirred for 2 hours with the exclusion of water. A teaspoonful of dehydrated Raney nickel and 15 g of molecular sieve 3 A were then added, the reaction mixture was briefly stirred and then hydrogenated for 22 hours under an H_2 atmosphere of 4 bar. The reaction mixture was filtered and concentrated to small volume. Conversion (according to HPLC), referred to 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 using concentrated HCl (for this purpose an aliquot was taken, diluted with water and the pH adjusted, then calculated for the total quantity). The solution was concentrated to 50 g under reduced pressure at 40°C, filtered through Celite and diluted with ethyl acetate to a total volume of 100 ml. 5.2 g of maleic acid dissolved in ethyl acetate + ethanol was added and seeded with Enalapril maleate. The crystallisate formed was separated and dried.

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Yield: 20.9 g = 85% of theoretical,
> 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 was suspended in 100 ml of ethanol. 75 mmol (15.5 g) of ethyl 2-oxo-4-phenylbutyrate and 18 g of molecular sieve 3 A were added thereto and the suspension was stirred for 2 hours with the exclusion of water. A teaspoonful of dehydrated Raney nickel and 15 g of molecular sieve 3 A were then added, the reaction mixture was briefly stirred and then hydrogenated for 22 hours under an H_2 atmosphere of 4 bar. The reaction mixture was filtered and concentrated to small volume. Conversion (according to HPLC), referred to 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 using concentrated HCl (for this purpose an aliquot was taken, diluted with water and the pH adjusted, then calculated for the total quantity). The solution was concentrated to 50 g under reduced pressure at 40°C, filtered through Celite and diluted with ethyl acetate to a total volume of 100 ml. 5.2 g of maleic acid dissolved in ethyl acetate + ethanol was added and seeded with Enalapril maleate. The crystallisate formed was separated and dried.

Yield: 7.4 g = 30% of theoretical,
> 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 was as in Example 1 but, instead of triethylamine, 0.8 moleq of ethanolamine was used as base. Conversion (according to HPLC), referred to ala-pro: 85%, product yield (according to HPLC): 85%, ratio of diastereoisomers prior to crystallisation: SSS:RSS isomers = 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) was taken up in 120 ml of n-butanol and approx. 50 ml of n-butanol was distilled off in a vacuum. The solution was diluted with 600 ml of ethanol. 22.5 g of molecular sieve 3 A, 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 teaspoonfuls of dehydrated Raney nickel were then added and the mixture was stirred for 4 hours in an H_2 atmosphere of 4 bar. After this period of time the pressure was released, an additional 12.4 g of ethyl 2-oxo-4-phenylbutyrate was added and stirring was continued for 2 hours. Then 4 bar H_2 was again applied and hydrogenation was carried out at this pressure for a further 4 hours. The catalyst was separated off (it can be reused directly) and the solution was evaporated. Conversion (according to HPLC), referred to N^{ϵ}-TFA-lys-pro: approx. 95%, product yield (according to HPLC): 90%, ratio of diastereoisomers prior to crystallisation: SSS:RSS isomers = 95:5. The residue was suspended in 450 ml of water and 450 ml of 1,1,1-trichloroethane at 5°C, a pH value of 9.6 was established in the aqueous phase by means of 50%

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NaOH and the phases were thoroughly mixed. The organic phase was separated off and the aqueous product phase was reextracted with 100 ml of 1,1,1-trichloroethane. At 5°C a pH value of 4.6 was then established in the aqueous phase and this was extracted twice with 400 ml of 1,1,1-trichloroethane. The organic phase was concentrated by evaporation 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 theoretical), content of SSS-diastereoisomer: > 99%, $[\alpha]_D^{20}$: -25.5° [(c=1 in MeOH/1N HCl (1:1)].

Example 4

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

The procedure was as in Example 4 but, instead of triethylamine, 0.2 moleq of tributylamine was used as base.
Conversion (according to HPLC), referred to N^{ϵ}-TFA-lys-pro: 85%,
product yield (according to HPLC): 75%,
ratio of diastereoisomers prior to crystallisation: SSS:RSS diastereoisomers = 96.4:3.6.

Example 5

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

The procedure was as in Example 4 but, instead of triethylamine, 0.8 moleq of ethanolamine was used as base.
Conversion (according to HPLC), referred to N^{ϵ}-TFA-lys-pro: 75%,
product yield (according to HPLC): 65%,

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ratio of diastereoisomers prior to crystallisation: SSS:RSS diastereoisomers = 93:7.

Example 6

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

The procedure was as in Example 4 but, instead of triethylamine, 0.2 moleq of L-prolinol was used as base.
Conversion (according to HPLC), referred to N^{ϵ}-TFA-lys-pro: 85%,
product yield (according to HPLC): 65%,
ratio of diastereoisomers prior to crystallisation: SSS:RSS diastereoisomers = 95:5.

Example 7

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

The procedure was as in Example 4 but, instead of triethylamine, 0.2 moleq of (1R, 2S)-(-)-ephedrine was used as base.
Conversion (according to HPLC), referred to N^{ϵ}-TFA-lys-pro: 84%,
product yield (according to HPLC): 70%,
ratio of diastereoisomers prior to crystallisation: SSS:RSS diastereoisomers = 96.7:3.3.

Example 8

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

The procedure was as in Example 4 but 0.1 moleq of triethylamine was used as base.

Conversion (according to HPLC), referred to N$^{\varepsilon}$-TFA-lys-pro: 75%,
product yield (according to HPLC): 60%,
ratio of diastereoisomers prior to crystallisation: SSS:RSS diastereoisomers = 97.7:2.3.

Example 9

N$^{\alpha}$-[(S)-1-ethoxycarbonyl-3-phenylpropyl]-N$^{\varepsilon}$-trifluoroacetyl-L-lysyl-L-proline

The procedure was as in Example 4 but, instead of molecular sieve and base, 25 g of basic activated aluminium oxide was used.
Conversion (according to HPLC), referred to N$^{\varepsilon}$-TFA-lys-pro: 95%,
product yield (according to HPLC): 80%,
ratio of diastereoisomers prior to crystallisation: SSS:RSS diastereoisomers = 95.5:4.5.

Example 10

N$^{\alpha}$-[(S)-1-ethoxycarbonyl-3-phenylpropyl]-N$^{\varepsilon}$-trifluoroacetyl-L-lysyl-L-proline

The procedure was as in Example 4 but, instead of Raney nickel, palladium 1% on carbon was used as catalyst.
Conversion (according to HPLC), referred to N$^{\varepsilon}$-TFA-lys-pro: 90%,
product yield (according to HPLC): 80%,
ratio of diastereoisomers prior to crystallisation: SSS:RSS diastereoisomers = 62:38.

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Example 11

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

250 mmol of L-alanine benzyl ester p-toluenesulphonate salt (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 250 mmol of N-methylmorpholine (25.3 g), the reaction mixture was azeotropically distilled, with removal of water, until the reaction was complete. After cooling, the mixture was removed from the salts by filtration, concentrated by evaporation and taken up in 400 ml of anhydrous methanol. After the addition of 25 mmol of N-methylmorpholine (1 g) and 3 teaspoonfuls of dehydrated Raney nickel, hydrogenation was carried out at 4 bar excess hydrogen pressure and room temperature until hydrogen uptake was complete. The reaction mixture was removed from the catalyst by filtration, washed with warm methanol and concentrated by evaporation. The residue was distributed between water and 1,1,1-trichloroethane at 5°C and pH 9.6. The aqueous phase was then extracted with 1,1,1-trichloroethane at pH 3 and 5°C and the organic phase was concentrated by evaporation. The residue was crystallised from ethanol or acetone in the cold.
Yield: first fraction: 35 g; second fraction: 12 g
Melting point: 143-145°C.

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Claims

1. Reductive amination of an amino acid or of an amino acid derivative using an α-keto acid or an α-keto acid derivative in an inert solvent in the presence of a hydrogenating catalyst and hydrogenating agent and optionally with the removal of water, with the reductive amination comprising the steps of imine formation and reduction to the amine, characterised in that the reductive amination, in the course of the imine formation and the reduction to the amine, is carried out in the presence of an excess of base.

2. Reductive amination according to claim 1, characterised in that the amino acid is an α-amino acid.

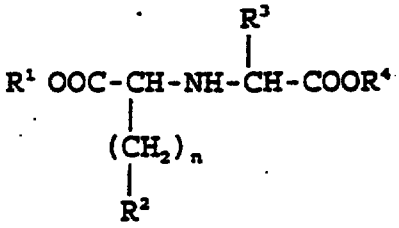
3. Reductive amination according to claim 1 or 2, characterised in that the amino acid derivative is an ester.

4. Reductive amination according to claim 1 or 2, characterised in that the amino acid derivative is an amide.

5. Reductive amination according to claim 4, characterised in that the amide is a peptide.

6. Reductive amination according to claim 3 or 5, characterised in that a compound of the formula





(I)

wherein

R^1 signifies hydrogen, methyl, ethyl or benzyl,

R^2 signifies hydrogen, C_1-C_4-alkyl, phenyl or phenyl-[C_1-C_4-alkyl],

R^3 signifies hydrogen, heteroalkyl or C_1-C_4-alkyl, benzyl, 4'-hydroxybenzyl, acylamino-[C_1-C_5]-alkyl, tert.-butyloxy-carbonylamino-[C_1-C_5]-alkyl, benzyloxycarbonylamino-[C_1-C_5]-alkyl,

R^4 signifies H or an ester protecting group,

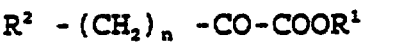
n is 0, 1 or 2,

is obtained by hydrogenolytic conversion of a compound of the formula



(III),

wherein R^3 and R^4 have one of the meanings already given, with a compound of the formula

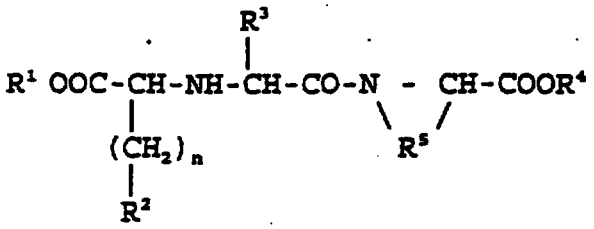


(V),

wherein R^1, R^2 and n have one of the meanings already given,

or that a compound of the formula

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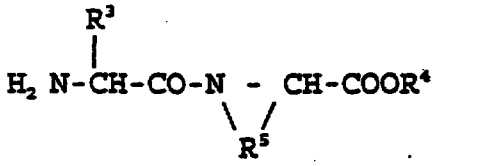


(II),

wherein R^1, R^2, R^3, R^4 and n have the meanings given above,

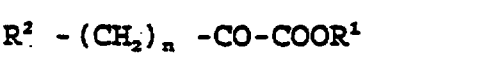
R^5 together with the atoms carrying it signifies a heterocyclic monocyclic or bicyclic ring system having 5 to 10 ring members,

is obtained by hydrogenolytic conversion of a compound of the formula



(IV),

wherein R^3 to R^5 have one of the meanings already given, with a compound of the formula



(V),

wherein R^1, R^2 and n have one of the meanings already given.

7. Method according to one of the preceding claims, characterised in that
the organic base used is mono-, di- or triethanolamine, trimethylamine, triethylamine, tripropylamine, tributylamine, n-methylmorpholine, L- or D-prolinol, L- or D-valinol, (-)- or (+)-ephedrine, (-)- or (+)-norephedrine.

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8. Method according to one of claims 1 to 6, characterised in that the inorganic base used is K_2CO_3, Na_2CO_3, $KHCO_3$, NaOAc, $NaHCO_3$, or basic aluminium oxide.

9. Method according to one of the preceding claims, characterised in that the base is used in a quantity of from 0.01 to 5 mole equivalents, preferably 0.05 to 2 mole equivalents, and particularly when organic bases are used, particularly preferably of from 0.08 to 0.6 mole equivalents, in each case referred to the compounds used having the formulae (III) or (IV).

10. Method according to claim 8 or 9, characterised in that the basic aluminium oxide is used in a quantity of from 2 g/mol to 400 g/mol, referred to the compounds used having the formulae (III) or (IV).

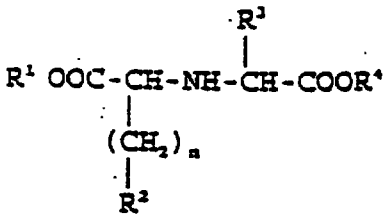
11. Method according to one of claims 1 to 6, characterised in that the basic aluminium oxide is used as a water-binding agent for the removal of water.

12. Method according to claim 11, characterised in that the basic aluminium oxide is used in a quantity of from 50 g/mol to 500 g/mol, referred to the compounds used having the formulae (III) or (IV).

REDUCTIVE AMINATION OF AN AMINO ACID OR AN AMINO ACID DERIVATIVE WITH AN ALPHA-KETO ACID OR AN ALPHA-KETO ACID DERIVATIVE

Description

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



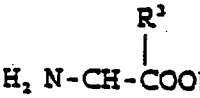
(I)

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wherein

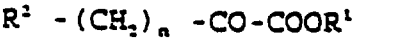
R^1 signifies hydrogen, methyl, ethyl or benzyl,
R^2 signifies C_1-C_4-alkyl, phenyl or phenyl-[C_1-C_4-alkyl],
R^3 signifies hydrogen, heteroalkyl or C_1-C_4-alkyl, benzyl, 4'-hydroxybenzyl, acylamino-[C_1-C_5]-alkyl, tert.-butyloxy-carbonylamino-[C_1-C_5]-alkyl, benzyloxycarbonylamino-[C_1-C_5]-alkyl,
R^4 signifies H or an ester protecting group,
n is 0, 1 or 2,

by hydrogenolytic conversion of a compound of the formula



(III),

wherein R^3 and R^4 have one of the meanings already given, with a compound of the formula



(V),