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(54) Title: PROCESS FOR THE EFFICIENT PREPARATION OF N-SUBSTITUTED DEHYDROAMINO ACID ESTERS

(57) Abstract

A process for the preparation of N-substituted dehydroamino acid esters by contacting a β-hydroxy-α-amino acid ester or N- or O-substituted β-hydroxy-α-amino acid ester with an excess of acetic anhydride and a base is disclosed.

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TITLE

PROCESS FOR THE EFFICIENT PREPARATION OF N-SUBSTITUTED DEHYDROAMINO ACID ESTERS

FIELD OF THE INVENTION

This invention relates to the preparation of N-substituted dehydroamino acid esters by dehydration of β-hydroxy-α-amino acid esters or N- or O-substituted β-hydroxy-α-amino acid esters.

BACKGROUND OF THE INVENTION

Dehydro α-amino acids are key intermediates for the manufacture of unnatural D-α-amino acids and non-proteinaceous α-amino acids using asymmetric hydrogenation technology. Such amino acids are increasingly important intermediates in the pharmaceutical, agrichemical, and flavor/fragrance industries. For example, the amino acid D-alanine is a component of an artificial sweetener alitame while non-proteinaceous 2-aminobutyric acid is a component of a tuberculostatic drug ethambutol. State-of-the-art asymmetric hydrogenation catalysts allow the manufacture of these α-amino acids with very high selectivity for a single enantiomer. For example, using rhodium catalysts bearing chiral phospholane ligands, the L- or D-isomer of alanine or 2-aminobutyric acid can be prepared from the corresponding dehydro amino acids in greater than 99% enantiomeric excess.

While aromatic dehydroamino acid derivatives such as dehydro phenylalanine are inexpensively available by the "Erlenmeyer synthesis", aliphatic analogous are more difficult to prepare. Of several methods devised to date, the most practical is the dehydration of the corresponding β-hydroxy-α-amino acid esters. Such routes avoid the use of expensive and hazardous reagents such as azides, t-butyl hypochlorite, pyruvic acid, or cysteine derivatives which are required in alternative

routes. The approach is especially attractive in cases where the necessary β-hydroxy-α-amino acid is inexpensively available. Moreover, the hydroxyamino acid starting material need not be enantiomerically pure. For example, readily available DL-serine can be converted to dehydroalanine while threonine gives the precursor for 2-amino butyric acid.

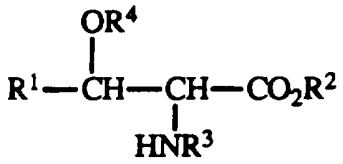
Existing procedures for the dehydration of β-hydroxy-α-amino acids fall into two categories, namely stepwise processes and direct dehydration procedures. In the stepwise routes, the hydroxyl group is often first converted to a better leaving group, typically the p-toluenesulfonate. Alternatively, the hydroxyl group has been O-diphenylphosphorylated for this purpose. Both procedures utilize moisture-sensitive derivatizing agents. Another stepwise process involves activation of the amine functionality by converting it to a cyclic diamide, followed by dehydration using the acidic catalyst potassium bisulfate. A. G. Brown and T. C. Smale, J. Chem. Soc., Perkin Trans. 1, 65 (1972). All of these stepwise procedures are inherently inefficient since they involve the isolation and purification of a reactive intermediate.

Most of the direct dehydration processes utilize expensive reagents such as diisopropylcarbodiimide/copper(I) chloride, N,N'-carbonyldiimidazole, or DAST (diethylaminosulfur trifluoride). An alternative procedure uses moderately expensive diethyl chlorophosphate but additionally requires the hazardous (pyrophoric) base sodium hydride to effect elimination.

Thus there is a need for an improved single step dehydration process which uses reagents which are readily available, inexpensive and non-hazardous. The present invention provides such a process.

SUMMARY OF THE INVENTION

This invention provides a process for the preparation of N-substituted dehydroamino acid esters comprising contacting a β-hydroxy-α-amino acid ester or an N- or O-substituted B-hydroxy-α-amino acid ester of formula I



I

wherein

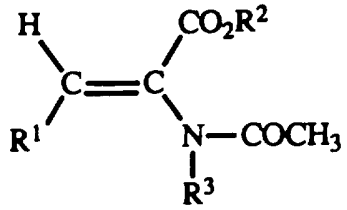
R^1 is hydrogen, C_3-C_{20} alkyl, C_1-C_{20} cycloalkyl, C_6-C_{14} aryl, C_7-C_{20} aralkyl or C_7-C_{20} alkylaryl optionally substituted with NR^5R^6, OR^5, COR^5, CNR^5R^6, or CN wherein R^5 and R^6 are each independently C_1-C_6 alkyl or C_6-C_{14} aryl;

R^2 is C_1-C_{20} alkyl, C_3-C_{20} cycloalkyl, C_6-C_{14} aryl, C_7-C_{20} aralkyl or C_7-C_{20} alkylaryl optionally substituted with NR^5R^6, OR^5, COR^5, CNR^5R^6, or CN wherein R^5 and R^6 are each independently C_1-C_6 alkyl or C_6-C_{14} aryl;

R^3 is hydrogen, C_1-C_{20} acyl, C_1-C_{20} alkyl, C_3-C_{20} cycloalkyl, C_6-C_{14} aryl, C_7-C_{20} aralkyl or C_7-C_{20} alkylaryl optionally substituted with NR^5R^6, OR^5, COR^5, CNR^5R^6, or CN wherein R^5 and R^6 are each independently C_1-C_6 alkyl or C_6-C_{14} aryl;

R^4 is H or C_1-C_{20} acyl;

with an excess of acetic anhydride and a base to yield an N-substituted dehydroamino acid ester of formula II



II

wherein R^1, R^2 and R^3 are as defined above in formula I.

DETAILED DESCRIPTION OF THE INVENTION

This invention provides a process for the preparation of N-substituted dehydroamino acid esters.

The term "acyl" as used herein denotes $\overset{O}{\overset{\|}{C}}R$ wherein R is hydrogen, C_1-C_{20} alkyl, C_6-C_{14} aryl, C_7-C_{20} aralkyl, C_7-C_{20} alkylaryl and their various isomers.

The term "alkyl" as used herein denotes a straight-chain or branched-chain alkyl such as methyl, ethyl, n-propyl, i-propyl, or the different butyl, pentyl, hexyl, and other isomers up to 20 carbon atoms.

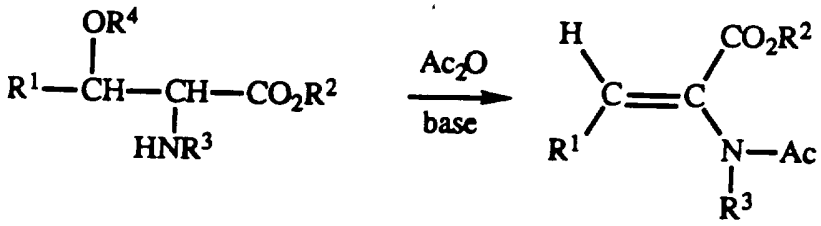
The term "cycloalkyl" denotes a cyclic alkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and others up to 20 carbon atoms.

The term "aryl" denotes aromatic groups such as phenyl, 1-naphthyl, 2-naphthyl, or biphenylyl.

The term "aralkyl" denotes aromatic groups having at least one alkyl substituent linked via a carbon atom of the aromatic group. Examples include benzyl, α-phenethyl and β-phenethyl.

The term "alkylaryl" denotes aromatic groups having at least one alkyl substituent linked via a carbon atom of the alkyl substituent. Examples include o-tolyl, m-tolyl, p-tolyl, and p-t-butylphenyl.

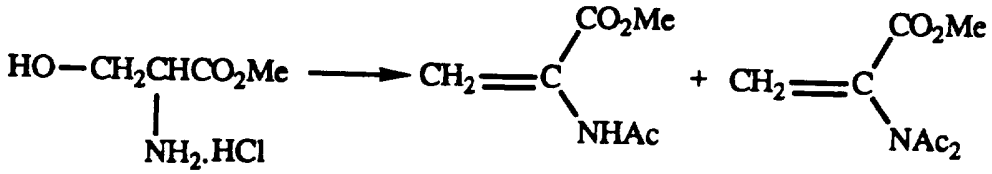
The process of the present invention for preparation of esters of N-substituted dehydroamino acid esters by contacting an β-hydroxy-α-amino acid ester or an N- or O-substituted β-hydroxy-α-amino acid ester with acetic anhydride and a base is shown in equation 1) below:

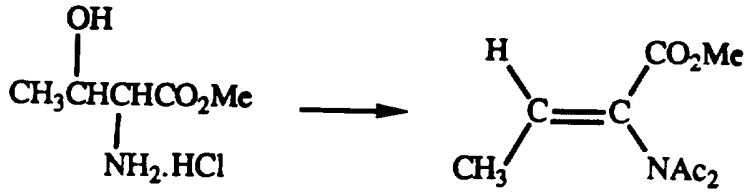
1) 

wherein

R^1, R^2, R^3, and R^4 are as defined above in formula I.

Examples include the preparation of methyl α-(N,N-diacetyl)amido acrylate (obtained as a mixture with the monoacetamide) from serine methyl ester shown in equation 2) below and the preparation of methyl α-(N,N-diacetyl)amido-Z-crotonate from threonine methyl ester, as shown in equation 3) below:

2) 

3) 

Bases suitable for use in the process of the present invention are inorganic or organic. The conjugate acid of said base has a pK_a in the range of about 4.75 to about 14, preferably 4.75 to about 10, most preferably 4.75 to 8. Examples of suitable

inorganic bases include various ester salts such as sodium acetate, potassium acetate, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate. Examples of suitable organic bases for the process of the present invention include tertiary amine bases. Examples include pyridine, picoline, diisopropylethylamine, triethylamine, tributylamine, N-methyl morpholine, DABCO (1,4-diazabicyclo[2.2.2]-octane), and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene). The molar ratio of base to reactant is from about 1:1 to about 30:1. Preferably the molar ratio of base to reactant is from about 1:1 to about 15:1. A range of 3:1 to 7:1 is most preferred.

The β-hydroxy-α-amino acid ester or N- or O-substituted β-hydroxy-α-amino acid ester starting materials of the process may be utilized as a free base or may be introduced as a salt such as a hydrochloride, sulfate, or oxalate salt. Many such compounds are available commercially or may be prepared by methods known in the art, as further demonstrated by Example 7 herein.

The process of the invention can be carried out at atmospheric pressure or at pressures between 100 and 1000 kP_a. Reaction at atmospheric pressure is preferred. The process is preferably carried out under air, but an inert atmosphere such as nitrogen or argon may be utilized.

The preferred solvent is excess acetic anhydride. However, organic co-solvents may optionally be used; examples of suitable organic co-solvents include toluene, xylene, chlorobenzene, pyridine, di-n-butyl ether, and dimethyl acetamide.

The reaction is carried out over a temperature range of from about 80°C to about 200°C. Preferably, the reaction is conducted at a temperature of from about

100°C to 180°C. A range of 120°C to 150°C is most preferred. Reaction times can vary from about 0.5 hour to about 48 hours. A time of 1 to 4 hours is preferred.

Agitation during the reaction is preferable since it is conducted under reflux conditions. The product is isolated using conventional techniques such as distillation, extraction, or chromatography. The product is obtained as a mono- or di-N-acetyl derivative, or a mixture thereof.

The current invention provides advantages over prior art processes in several respects. The reagents used for dehydration, preferably acetic anhydride and a base such as sodium acetate or pyridine, are cheap and relatively innocuous. No separate step is required either to protect the amine functionality or to activate the hydroxyl group toward elimination. The product dehydro-α-amino acid is obtained as a mono- or di-N-acetyl derivative; the acetyl group is a suitable directing group for subsequent asymmetric hydrogenation.

The process of the present invention is useful for the preparation of dehydroamino esters. Such esters are useful starting materials in asymmetric hydrogenation reactions to prepare particular isomers of α-amino acids of importance in the pharmaceutical, agrichemical, and flavor/fragrance industries.

The following Examples demonstrate the process of the invention. The amino acid starting materials used in these examples are commercially available from Sigma Chemical Company, St. Louis, MO.

EXAMPLE 1

A mixture of DL-serine methyl ester hydrochloride (15.6 g, 100 mmol), pyridine (50 mL), and acetic anhydride (100 mL) was heated at reflux for 2 hours. Excess solvent was removed at reduced pressure. The residue was added to water (250 mL) and was extracted

into ether (500 mL). The ether phase was stirred 1 hour with saturated aqueous sodium bicarbonate (100 mL), washed with water (50 mL), and dried with magnesium sulfate. Removal of ether at reduced pressure afforded 8.40 g of an amber oil which was shown to be a mixture of methyl α-acetamido acrylate and methyl α-(N,N-diacetyl)amido acrylate by NMR spectroscopy. A portion of this product was vacuum distilled to afford material (3.01 g) boiling at 63-72°C at 0.5 torr (66.7 pa) which was enriched in methyl α-acetamido acrylate and a fraction (2.28 g) boiling at 72-74°C which was shown to be substantially pure methyl α-(N,N-diacetyl)amido acrylate by ^{1}H and ^{13}C NMR. For the diamide ^{1}H NMR ($CDCl_3$/TMS): σ 2.36 (s, 6H), 3.83 (s, 3H), 5.82 (s, 1H), 6.60 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS): σ 25.97, 52.90, 128.00, 137.16, 163.30, 172.10. For the monoamide ^{1}H NMR ($CDCl_3$/TMS): σ 2.15 (s, 3H), 3.84 (s, 3H), 5.90 (s, 1H), 6.60 (s, 1H), 7.81 (broad s, 1H); ^{13}C NMR ($CDCl_3$/TMS): σ 24.66, 52.96, 108.66, 130.82, 164.55, 168.77.

EXAMPLE 2

A mixture of L-threonine methyl ester hydrochloride (17.0 g, 100 mmol), pyridine (50 mL), and acetic anhydride (100 mL) was heated at reflux for 2 hours. Excess solvent was removed at reduced pressure. The residue was added to water (250 mL) and was extracted into ether (500 mL). The ether phase was stirred 1 hour with saturated aqueous sodium bicarbonate (100 mL), washed with water (50 mL), and dried with magnesium sulfate. Removal of ether at reduced pressure afforded a residue which was distilled (76-82°C at 0.25 torr (33.3 pa)) to afford methyl α-(N,N-diacetyl)amido-Z-crotonate (11.95 g, 60%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$/TMS): σ 1.80 (d, J=7, 3H), 2.32 (s, 6H), 3.80

(s, 3H), 7.22 (q, J=7, 1H); ^{13}C NMR ($CDCl_3$/TMS): σ 13.37, 25.44, 52.35, 130.66, 140.36, 163.52, 171.73.

EXAMPLE 3

A round-bottomed flask was charged with L-threonine methyl ester hydrochloride (17.0 g, 0.10 mol), anhydrous sodium acetate (50 g, 0.61 mol), and acetic anhydride (150 mL). After heating at reflux for 2 hours, volatiles were removed at reduced pressure. The residue was taken up in ether (250 mL) and was washed twice with water (250 mL, 50 mL). Volatiles were removed at reduced pressure and the residue was distilled at 86-90°C at 0.4 torr (53.3 pa) to give α-(N,N-diacetyl)-amido-Z-crotonate (13.82 g, 69%) as a pale yellow liquid. ^1H NMR ($CDCl_3$/TMS): σ 1.80 (d, J=7, 3H), 2.32 (s, 6H), 3.80 (s, 3H), 7.22 (q, J=7, 1H); ^{13}C NMR ($CDCl_3$/TMS): σ 13.37, 25.44, 52.35, 130.66, 140.36, 163.52, 171.73.

EXAMPLE 4

A mixture of crushed anhydrous potassium carbonate (5.0 g, 35 mmol), L-threonine methyl ester hydrochloride (1.70 g, 10 mmol), and acetic anhydride (15 mL) was heated at reflux for 2 hours. Upon cooling the resultant solid mass was stirred with ether (25 mL) and water (25 mL). The ether layer was washed with additional water (5 mL) and volatiles were distilled off at reduced pressure to afford 1.17 g of a red oil. This crude residue was shown by NMR spectroscopy to contain, in addition to some unreacted acetic anhydride, α-(N,N-diacetyl)amido-Z-crotonate as the principal component. ^1H NMR ($CDCl_3$/TMS): σ 1.80 (d, J=7, 3H), 2.32 (s, 6H), 3.80 (s, 3H), 7.22 (q, J=7, 1H); ^{13}C NMR ($CDCl_3$/TMS): σ 13.37, 25.44, 52.35, 130.66, 140.36, 163.52, 171.73.

EXAMPLE 5

A mixture of sodium bicarbonate (5.0 g, 60 mmol), DL-serine methyl ester hydrochloride (1.56 g, 10 mmol),

and acetic anhydride (15 mL) was heated at reflux for 2 hours. Upon cooling the resultant mixture was stirred with ether (25 mL) and water (25 mL). The ether layer was washed with additional water (5 mL) and volatiles were distilled off at reduced pressure to afford 1.17 g of an amber liquid. A few crystals of hydroquinone were added to inhibit polymerization. The crude residue was shown by NMR spectroscopy to contain, in addition to some unreacted acetic anhydride, a mixture of methyl α-acetamido acrylate and methyl α-(N,N-diacetyl)amido acrylate in a roughly 2:3 molar ratio. For the diamide ^{1}H NMR ($CDCl_3$/TMS): σ 2.36 (s, 6H), 3.83 (s, 3H), 5.82 (s, 1H), 6.60 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS): σ 25.97, 52.90, 128.00, 137.16, 163.30, 172.10. For the monoamide ^{1}H NMR ($CDCl_3$/TMS): σ 2.15 (s, 3H), 3.84 (s, 3H), 5.90 (s, 1H), 6.60 (s, 1H), 7.81 (broad s, 1H); ^{13}C NMR ($CDCl_3$/TMS): σ 24.66, 52.96, 108.66, 130.82, 164.55, 168.77.

EXAMPLE 6

A mixture of serine benzyl ester hydrochloride (4.63 g, 20 mmol), sodium acetate (10 g, 12 mmol), and acetic anhydride (30 mmol) was heated at reflux for 2 hours. Volatiles were removed at reduced pressure and the residue was taken up in ether and washed (50 mL each). The ether layer was washed with additional water (10 mL) and the volatiles were removed at reduced pressure to afford 5.83 g of crude product as an amber liquid. The residue was purified by flash chromatography on silica using 3:1 hexane/ethyl acetate as solvent. The product obtained in this way (4.44 g, 88%) was a 3:1 mixture of benzyl α-acetamido acrylate and benzyl α-(N,N-diacetyl)amino acrylate and its identity was confirmed by ^{1}H and ^{13}C NMR spectroscopy. For the diamide ^{1}H NMR ($CDCl_3$/TMS): σ 2.33 (s, 6H), 5.25 (s, 2H), 5.82 (s, 1H), 6.62 (s, 1H), 7.3-7.4 (m,

5H). For the monoamide ^1H NMR ($CDCl_3$/TMS): σ 2.11 (s, 3H), 5.26 (s, 2H), 5.94 (s, 1H), 6.60 (s, 1H), 7.3-7.4 (m, 5H), 7.76 (broad s, 1H). For the mixture of diamide and monoamide ^{13}C NMR ($CDCl_3$/TMS): σ 24.58, 25.93, 67.64, 67.72, 108.90, 128.04, 128.12, 128.20, 128.46, 128.53, 128.60, 130.91, 135.02, 135.05, 137.19, 162.65, 163.92, 168.82, 172.08.

EXAMPLE 7

A mixture of N,O-diacetyl DL-threonine methyl ester (2.07 g, 9.5 mmol), pyridine (5 mL), and acetic anhydride (10 mL) was heated at reflux for 2 hours. Volatiles were distilled off at reduced pressure and the residue was taken up in ether (50 mL). The ether solution was washed twice with water (25 mL) and the volatiles were removed at reduced pressure. The resultant red oil was shown by NMR spectroscopy to contain, in addition to some unreacted acetic anhydride, α-(N,N-diacetyl)amido-Z-crotonate as the principal component. ^1H NMR ($CDCl_3$/TMS): σ 1.80 (d, J=7, 3H), 2.32 (s, 6H), 3.80 (s, 3H), 7.22 (q, J=7, 1H); ^{13}C NMR ($CDCl_3$/TMS): σ 13.37, 25.44, 52.35, 130.66, 140.36, 163.52, 171.73.

The N,O-diacetyl DL-threonine methyl ester employed as a starting material in this example was prepared as follows: A mixture of threonine methyl ester hydrochloride (5 g), pyridine (15 mL), and acetic anhydride (15 mL) was stirred at room temperature overnight. Volatiles were removed at reduced pressure and the residue was added to ether (200 mL). The resultant ether solution was decanted away from the solid precipitate and the solvent was distilled at reduced pressure to give crude product which was crystallized from toluene to give the desired product (2.26 g) as a white crystalline solid, mp 112°C. ^1H NMR ($CDCl_3$/TMS): σ 1.27 (d, J=7, 3H), 2.03 (s, 3H), 2.10

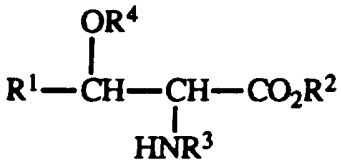
(s, 3H), 3.73 (s, 3H), 4.80 (dd, J=3, 12, 1H), 5.43 (dq, J=3, 7, 1H), 6.17 (broad d, J=12, 1H); ^{13}C NMR ($CDCl_3$/TMS): σ 17.30, 21.09, 23.32, 52.90, 55.56, 70.60, 169.85, 170.50, 170.60.

EXAMPLE 8

A mixture of DL-serine methyl ester hydrochloride (15.6 g, 0.1 mol), diisopropylethylamine (50 mL), and acetic anhydride (100 mL) were heated at reflux for 2 hours. The volatiles were distilled off at high vacuum and the residue was taken up in ether (500 mL) and washed with 1 N HCl (100 mL). Saturated aqueous sodium bicarbonate (100 mL) was added and the mixture was stirred 1 hour. The ether layer was washed with water (50 mL) and was dried over magnesium sulfate. The solvent was removed at reduced pressure and the red liquid residue was distilled to afford a fraction (4.00 g) boiling at 60-65°C at 0.5 torr (66.7 pa) which was enriched in methyl α-acetamido acrylate and a fraction (5.57 g) boiling at 87-97°C at 1.2 torr (160 pa) which was shown to be substantially pure methyl α-(N,N)-diacetyl)amido acrylate by ^{1}H and ^{13}C NMR. For the diamide ^{1}H NMR ($CDCl_3$/TMS): σ 2.36 (s, 6H), 3.83 (s, 3H), 5.82 (s, 1H), 6.60 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS): σ 25.97, 52.90, 128.00, 137.16, 163.30, 172.10. For the monoamide ^{1}H NMR ($CDCl_3$/TMS): σ 2.15 (s, 3H), 3.84 (s, 3H), 5.90 (s, 1H), 6.60 (s, 1H), 7.81 (broad s, 1H); ^{13}C NMR ($CDCl_3$/TMS): σ 24.66, 52.96, 108.66, 130.82, 164.55, 168.77.

What is claimed is:

1. A process for the preparation of N-substituted dehydroamino acid esters comprising contacting a β-hydroxy-α-amino acid ester or N- or O-substituted β-hydroxy-α-amino acid ester of formula I



I

wherein

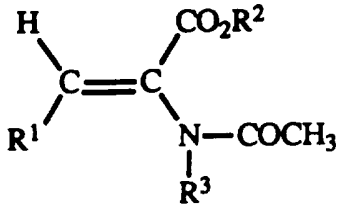
R^1 is hydrogen, C_1-C_{20} alkyl, C_3-C_{20} cycloalkyl, C_6-C_{14} aryl, C_7-C_{20} aralkyl or C_7-C_{20} alkylaryl optionally substituted with NR^5R^6, OR^5, COR^5, CNR^5R^6, or CN wherein R^5 and R^6 are each independently C_1-C_6 alkyl or C_6-C_{14} aryl;

R^2 is C_1-C_{20} alkyl, C_3-C_{20} cycloalkyl, C_6-C_{14} aryl, C_7-C_{20} aralkyl or C_7-C_{20} alkylaryl optionally substituted with NR^5R^6, OR^5, COR^5, CNR^5R^6, or CN wherein R^5 and R^6 are each independently C_1-C_6 alkyl or C_6-C_{14} aryl;

R^3 is hydrogen, C_1-C_{20} acyl, C_1-C_{20} alkyl, C_3-C_{20} cycloalkyl, C_6-C_{14} aryl, C_7-C_{20} aralkyl or C_7-C_{20} alkylaryl optionally substituted with NR^5R^6, OR^5, COR^5, CNR^5R^6, or CN wherein R^5 and R^6 are each independently C_1-C_6 alkyl or C_6-C_{14} aryl;

R^4 is H or C_1-C_{20} acyl;

with an excess of acetic anhydride and a base to yield an N-substituted dehydroamino acid ester of formula II



II

wherein R^1, R^2 and R^3 are as defined above in formula I.

2. The process of Claim 1 further comprising a cosolvent selected from the group consisting of toluene, xylene, chlorobenzene, pyridine, di-n-butyl ether or dimethyl acetamide.

3. The process of Claim 1 wherein the base is an inorganic or organic base the conjugate acid of which has a pK_a of from about 4.75 to about 14.

4. The process of Claim 4 wherein the base is selected from the group consisting of sodium acetate, potassium acetate, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, pyridine, picoline, diisopropylethylamine, triethylamine, tributylamine, N-methyl morpholine, 1,4-diazabicyclo[2,2,2]octane, and 1,8-diazabicyclo[5,4,0]undec-7-ene.

5. The process of Claim 3 wherein the molar ratio of base to reactant is from about 1:1 to about 30:1.

6. The process of Claim 5 wherein the molar ratio of base to reactant is from about 3:1 to about 7:1.

7. The process of Claim 1 conducted at a temperature of from about 80°C to about 200°C.

8. The process of Claim 1 wherein formula II is methyl α-(N,N-diacetyl)amido acrylate or methyl α-(N,N-diacetyl)amido-Z-crotonate.

INTERNATIONAL SEARCH REPORT

Interr al Application No
PCT/US 95/14788

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C231/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB,A,625 949 (MERCK & CO) 10 March 1947 see the whole document	1-8
A	TETRAHEDRON LETT. (TELEAY);76; (12); PP.891-4, UTAH STATE UNIV.;DEP. CHEM. BIOCHEM.; LOGAN; UTAH, SRINIVASAN A ET AL 'Comments on assignment of stereochemistry to 2-acylaminocrotonates' see page 893	1-8

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 February 1996	08.03.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Sánchez García, J.M.

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INTERNATIONAL SEARCH REPORT

Interr al Application No
PCT/US 95/14788

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEM. BER. (CHBEAM,00092940);84; VOL.117 (4); PP.1497-512, UNIV. STUTTGART;INST. ORG. CHEM.; STUTTGART; D-7000/80; FED. REP. GER. (DE), EFFENBERGER F ET AL 'Amino Acids, 2. N-Acetyl.alpha.,.beta.-didehydro.alpha.-amino acid esters from.alpha.-azidocarboxylic acid esters by nitrogen elimination with rhenium catalysts' see page 1497 - page 1498 ---	1-8
A	DE,A,27 18 552 (SUMITOMO CHEMICAL CO) 10 November 1977 see claims ---	1-8
A	EP,A,0 195 201 (DEGUSSA) 24 September 1986 see claims -----	1-8

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter ..al Application No
PCT/US 95/14788

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GB-A-625949		NONE		
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		JP-A-	52133905	09-11-77
		JP-B-	61006812	01-03-86
		CH-A-	630339	15-06-82
		FR-A,B	2349567	25-11-77
		GB-A-	1526683	27-09-78
		NL-A-	7704627	01-11-77
		US-A-	4137417	30-01-79
		US-A-	4194050	18-03-80
EP-A-0195201	24-09-86	DE-A-	3508564	11-09-86
		CA-A-	1277988	18-12-90
		JP-A-	61212546	20-09-86