



(51) International Patent Classification:

C07C 231/02 (2006.01) C07C 231/12 (2006.01)
C07C 209/06 (2006.01) C07C 237/06 (2006.01)
C07C 229/08 (2006.01)

(21) International Application Number:

PCT/EP2011/062497

(22) International Filing Date:

21 July 2011 (21.07.2011)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

10170670.3 23 July 2010 (23.07.2010) EP

(71) Applicant (for all designated States except US): **Sandoz AG** [CH/CH]; Lichtstraße 35, CH-4056 Basel (CH).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **ALBERT, Martin** [AT/AT]; Dorf 23d, A-6260 Bruck am Ziller (AT). **DE SOUZA, Dominic** [AT/AT]; Pürstling 5, A-4844 Regau (AT). **LANGNER, Martin** [DE/AT]; Ludwig-Weinold-Weg 10, A-6330 Kufstein (AT).(74) Agent: **BERRYMAN, Natalia**; Vossius & Partner (No. 31), Siebertstraße 4, 81675 München (DE).

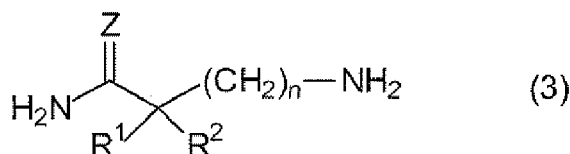
(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report (Rule 48.2(g))

(54) Title: METHOD FOR THE PREPARATION OF OMEGA-AMINO-ALKANEAMIDES AND OMEGA-AMINO-ALKANETHIOAMIDES AS WELL AS INTERMEDIATES OF THIS METHOD



(57) Abstract: The present invention relates to method for the preparation of an ω -amino-alkane(thio)amide having the formula (3). Furthermore, novel intermediates and partial reaction steps of the claimed method are disclosed.

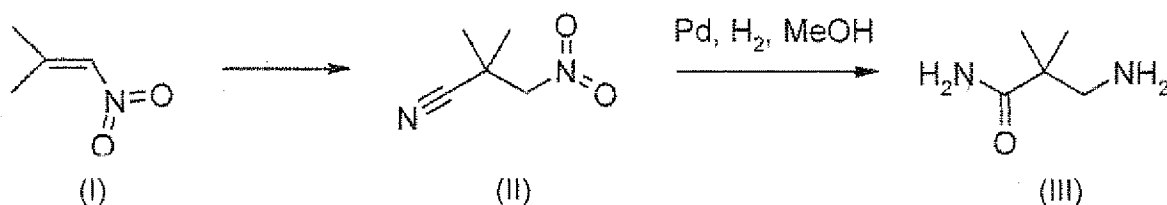
METHOD FOR THE PREPARATION OF ω -AMINO-ALKANEAMIDES AND ω -AMINO-ALKANETHIOAMIDES AS WELL AS INTERMEDIATES OF THIS METHOD

FIELD OF THE INVENTION

The present invention relates to methods for the preparation of ω -amino-alkaneamides and ω -amino-alkanethioamides. Certain intermediates and partial reaction steps of the methods are also claimed. The ω -amino-alkaneamides and ω -amino-alkanethioamides, in particular 3-amino-2,2-dimethylpropionamide, are of particular use in the synthesis of pharmaceuticals such as aliskiren. Aliskiren is a renin inhibitor, which can be used for the treatment of high blood pressure.

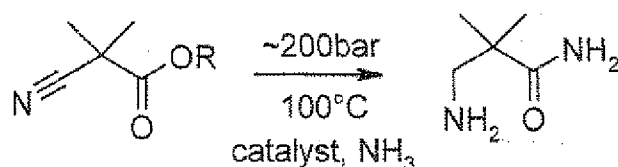
BACKGROUND OF THE INVENTION

3-Amino-2,2-dimethylpropionamide (compound (III), scheme 1) was first disclosed in Buckley; G. D.; Heath; R. L.; Rose; J. D. *J. Chem. Soc.* **1947**, 1500-1504. The process makes use of a conjugate addition of cyanide to nitroalkene (I). The resulting nitroalkane (II) is further reduced to compound (III) using Pd as a catalyst in the presence of H₂. The starting material (I) is accessed in a three step sequence from acetone and nitromethane.



Scheme 1: Preparation of 3-amino-2,2-dimethylpropionamide (III) according to Buckley *et al.*

A shorter process is described in WO 2007/071626. Herein, the reduction of a cyanoalkane acid ester such as (IV) using high pressure hydrogenation is disclosed. The conditions required for this conversion are rather harsh thereby limiting the broad applicability of this process. A similar approach using Rh/Al₂O₃ as a catalyst has been disclosed in WO 2006/013094. Here the formation of the amide occurs prior to the reduction of the nitrile.

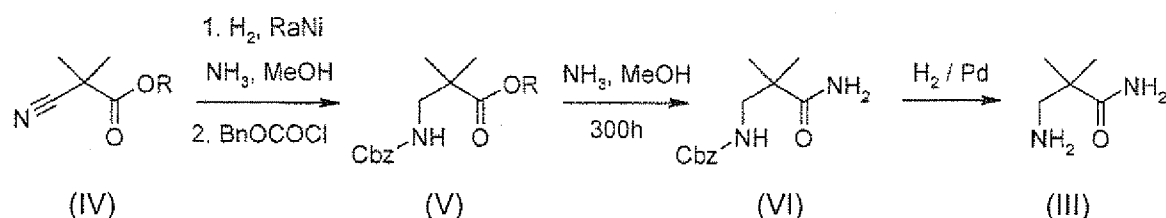


(IV)

(III)

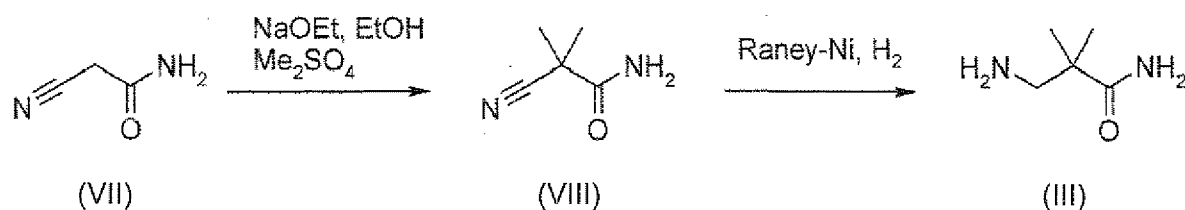
Scheme 2: Process for the preparation of (III) described in WO 2007/071626 (R = CH₃).

Another variation of this process has been published in Maibaum J., *J. Med. Chem.* **2007**, 50, 4832-4844. Compound (IV) (R = CH₂CH₃) serves as a starting material. The reduction of the nitrile is performed with H₂ using Raney nickel as a catalyst. The amino group is protected prior to the formation of the amide. The amide formation is slow (300 hours) and gives compound (VI) in moderate yield (53 % yield). Hydrogenolytic cleavage of the benzyloxycarbonyl (Cbz)-group gives compound (III) (scheme 3).



Scheme 3: Process for the preparation of (III) described in *J. Med. Chem.* **2007**, 50, 4832-4844.

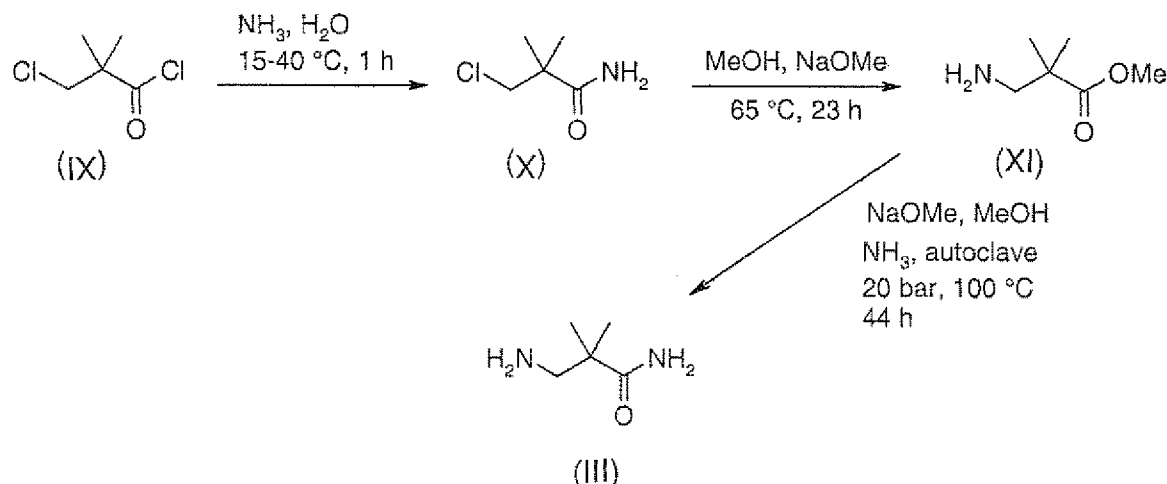
In a similar process (CN 1990461A; see scheme 4) 3-amino-2,2-dimethyl-propionamide (III) is prepared by hydrogenation of cyanodimethylacetic acid amide (VIII), which in turn is accessed by the alkylation of cyanoacetic acid amide (VII). Again, high pressure hydrogenation has to be applied to reduce the cyano group to the aminomethyl group. Additionally, the synthesis of compound (VIII) requires a costly alkylation of cyanoacetic acid amide.



Scheme 4: Process for the preparation of (III) described in CN 1990461.

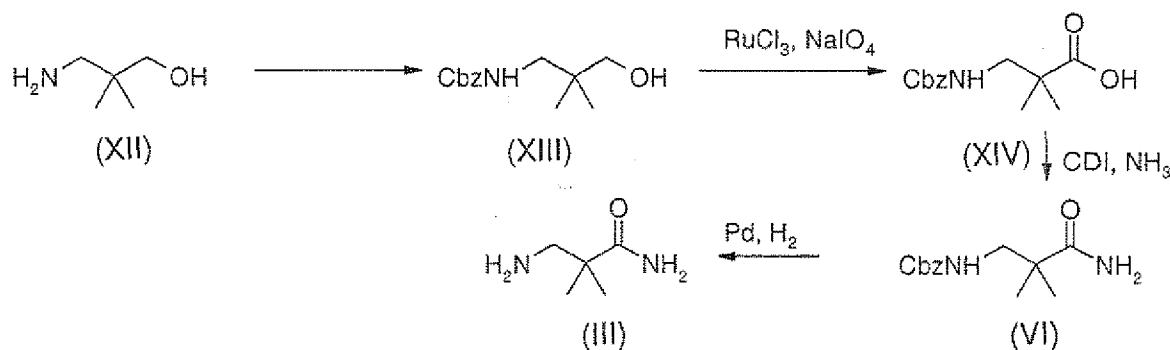
A variation of this process using protecting groups has been published by Dong, H. et al. in *Tetrahedron Lett.* **2005**, 46, 6337-6340.

A different approach for the synthesis of compound (III) avoiding any kind of hydrogenation has been disclosed in AT 502 804 (scheme 5). Though the process does not require a hydrogenation step, the conversion of (XI) to (III) has to be run in high pressure equipment in order to achieve reasonable reaction times. The overall yield of the desired product is rather low as the last two steps (from (X) to (XI) and (XI) to (III)) have a yield of less than 50% each resulting in an overall yield from (IX) to (III) of less than 25%.



Scheme 5: Process for the preparation of (III) described in AT 502 804.

In EP-A-1 548 024 (scheme 6) a process is disclosed which uses an elaborate protecting group strategy combined with an oxidation to give compound (III). Due to the length of the synthetic sequence and the use of costly catalysts the process is not suitable for commercial production of compound (III).



Scheme 6: Process for the preparation of (III) described in EP-A-1 548 024.

In view of the above, it was an object of the present invention to provide a method for the preparation of ω -amino-alkaneamides and ω -amino-alkanethioamides having the formula (3) and in particular 3-amino-2,2-dimethylpropionamide having the formula (3') which can provide the product in a good yield. Furthermore, the method should be amenable for production on an industrial scale. In the following the ω -amino-alkaneamide and ω -amino-alkanethioamide are generally referred to as ω -amino-alkane(thio)amide.

SUMMARY OF THE INVENTION

The invention is summarized in the appended claims.

Brief description of the figures:

Figure 1 is a scheme showing the reactions of the present invention.

Figure 2 is a scheme showing the preferred reactions of the present invention.

DEFINITIONS

Unless defined otherwise, the following definitions apply within the context of the present invention. It is self-evident that the specific compounds which are employed in the individual reactions steps must permit the desired reaction step to proceed and should not interfere with the desired reaction or lead to undesired by-products.

An "alkyl group" preferably refers to a C₁₋₈ alkyl group (e.g., methyl, ethyl, isopropyl, butyl, pentyl, hexyl, heptyl, and octyl), more preferably to a C₁₋₄ alkyl group (e.g., methyl, ethyl, propyl, and butyl). The alkyl group can be straight or branched.

An "acyl group" is defined as -C(O)-.

"Halogen" refers to F, Cl, Br, and I, preferably to Cl and Br.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a method for the preparation of an ω -amino-alkane(thio)amide (3). In a preferred embodiment the ω -amino-alkane(thio)amide is 3-amino-2,2-dimethylpropionamide (3'). Certain intermediates and partial reaction steps of the methods are also disclosed.

A scheme showing the reaction steps of the present invention is shown in Figure 1. In this figure and throughout the present application the following definitions apply.

Z is O or S, preferably Z is O.

R¹ is selected from the group consisting of H and C₁₋₈ alkyl. Preferably R¹ is C₁₋₄ alkyl, more preferably R¹ is methyl.

R² is selected from the group consisting of H and C₁₋₈ alkyl. Preferably R² is C₁₋₄ alkyl, more preferably R² is methyl.

In the present application at most one of R¹ and R² is H. Preferably R¹ and R² are C₁₋₄ alkyl, more preferably R¹ and R² are methyl.

R is C₁₋₈ alkyl, preferably R is C₁₋₄ alkyl, more preferably R is methyl.

n is an integer from 1 to 5. In a preferred embodiment n is 1 or 2 and in a more preferred embodiment n is 1.

X¹ is selected from the group consisting of halogen and R'-C(O)-O-, wherein R' is a C₁₋₈ alkyl group, preferably a C₁₋₄ alkyl group. Preferably X¹ is halogen, more preferably chlorine.

X² is a leaving group. The type of leaving group is not particularly limited but is preferably selected from the group consisting of halogen; -OSO₂R", wherein R" is a C₁₋₄ alkyl group which is optionally substituted with one or more halogens (e.g., mesylate or triflate) or wherein R" is a C₅₋₁₂ aryl which is optionally substituted with C₁₋₄ alkyl, NO₂ or CN (e.g., tosylate). Preferably X² is halogen, more preferably X² is chlorine.

X³ is a leaving group. The type of leaving group is not particularly limited but is preferably selected from the group consisting of halogen; -OSO₂R", wherein R" is a C₁₋₄ alkyl group which is optionally substituted with one or more halogens (e.g., mesylate or triflate) or wherein R" is a C₅₋₁₂ aryl which is optionally substituted with C₁₋₄ alkyl, NO₂ or CN (e.g., tosylate). Preferably X³ is halogen, more preferably X³ is bromine.

Every combination of each of the embodiments and preferred embodiments mentioned for Z, R¹, R², R, R', R", n, X¹, X² and X³ is also envisaged.

In one embodiment Z is O; R¹ is C₁₋₄ alkyl; R² is C₁₋₄ alkyl; and n is 1 or 2.

In another embodiment Z is O; R¹ is C₁₋₄ alkyl; R² is C₁₋₄ alkyl; n is 1 or 2; X² is halogen and optionally, if applicable, X¹ is halogen.

In another embodiment Z is O; R¹ is C₁₋₄ alkyl; R² is C₁₋₄ alkyl; n is 1 or 2; R is C₁₋₄ alkyl and optionally, if applicable, X² is halogen and optionally, if applicable, X¹ is halogen.

In a further embodiment Z is O; R¹ is C₁₋₄ alkyl; R² is C₁₋₄ alkyl; and n is 1 or 2; R is C₁₋₄ alkyl and optionally, if applicable, X³ is halogen.

In one embodiment Z is O; R¹ is methyl; R² is methyl; and n is 1.

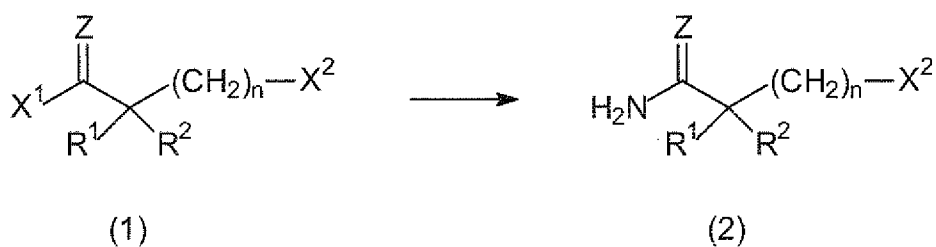
In another embodiment Z is O; R¹ is methyl; R² is methyl; and n is 1; X² is halogen (preferably chlorine) and optionally, if applicable, X¹ is halogen (preferably chlorine). If applicable, preferably both X¹ and X² are chlorine.

In another embodiment Z is O; R¹ is methyl; R² is methyl; and n is 1; R is methyl and optionally, if applicable, X² is halogen (preferably chlorine) and optionally, if applicable, X¹ is halogen (preferably chlorine). If applicable, preferably both X¹ and X² are chlorine.

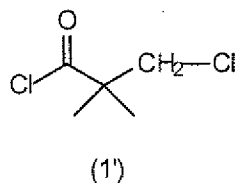
In a further embodiment Z is O; R¹ is methyl; R² is methyl; and n is 1; R is methyl and optionally, if applicable, X³ is halogen (preferably bromine).

Step A:

In step A the compound having the formula (2) is prepared by reacting a compound having the formula (1) with ammonia to form a compound having the formula (2):



The starting material (1) is commercially available or can be prepared by standard procedures which are known in the art. A preferred starting material is chloropivalic acid chloride (1').



The reaction conditions for step A are not particularly limited as long as the compound having the formula (1) reacts with ammonia to the compound having the formula (2).

In one embodiment step A can be conducted as described in AT-A-502 804. In this embodiment the compound having the formula (1) is reacted with ammonia. The ammonia can be supplied in gaseous form or in solution. The ammonia can be used in molar excess, preferably it can be employed in an amount of about 1 to about 30 mol, more preferably in an amount of about 1 to about 20 mol, preferably about 1.5 to about 5 mol, more preferably about 1.9 to about 2.5 mol, per 1 mol of the compound having the formula (1).

The reaction is optionally conducted in an organic solvent such as C₂₋₄ acetates, ethers, hydrocarbons, or alcohols. However, it is also possible to use water or a combination of an organic solvent and water as a reaction medium. In this embodiment, as illustrated in AT-A-502 804, the reaction is conducted in a biphasic system.

The reaction temperature is in the range of about 0 to about 100 °C, preferably about 5 to about 60 °C, more preferably about 15 to about 50 °C.

The pressure is in the range of about 1 to about 50 bar, preferably about 1 to about 10 bar, more preferably ambient pressure.

If desired, the compound having the formula (2) can be isolated and/or purified. Alternatively, it can be used in a subsequent reaction step without being isolated and/or without being purified.

Further details of this embodiment can be taken from AT-A-502 804.

In an alternative embodiment the compound having the formula (2) is prepared by reacting a compound having the formula (1) with ammonia to form a compound having the formula (2) in a homogeneous reaction medium. In the present invention a homogeneous reaction medium means a reaction medium having a single phase. The reaction medium is not particularly limited as long as it provides a homogeneous reaction medium for the specific

compounds (1) and (2). Typical examples are halogenated organic solvents such as halogenated C₁₋₄ alkanes (e.g., methylene chloride). Preferred solvents are halogenated C₁₋₄ alkanes, particularly methylene chloride.

The ammonia can be supplied in gaseous form or in solution. The ammonia is usually employed in molar excess. If ammonia is used in gaseous form it is typically passed through the reaction medium in order to provide the molar excess. A molar excess of, for example, about 1.1 to about 50 mol, preferably about 2 to about 40 mol, per 1 mol of the compound having the formula (1).

The reaction can be conducted at a temperature in the range of about -50 °C to about 50 °C, preferably about -10°C to about 20°C, more preferably about 0 °C to about 5 °C.

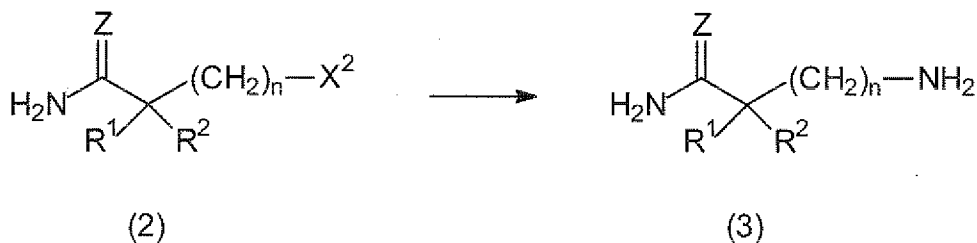
The duration of the reaction is typically from about 30 min to about 1 day, more typically about 1 hour to about 5 hours.

If desired, the compound having the formula (2) can be isolated and/or purified. Alternatively, it can be used as such in a subsequent reaction. Typical work-up procedures involve the removal of NH₄X¹, e.g., by filtration, centrifugation, washing with water, etc. The compound having the formula (2) can be (re)crystallized, if desired.

The present embodiment, in which homogeneous conditions are employed, is advantageous compared to the embodiment according to AT-A-502 804, in which biphasic conditions are employed, because it allows for simplified purification of the compound having the formula (2).

Step B:

The compound having the formula (2) is reacted with ammonia in the presence of a base to form the compound having the formula (3) in step B:



This reaction is conducted in a single step. The ammonia can be supplied in gaseous form or in solution. The ammonia is employed in an amount of about 5 to about 20 mol, preferably about 8 to about 12 mol, most preferably 10 mol per 1 mol of the compound having the formula (2).

The base is not particularly restricted. Typical bases are metallic hydrides, such as alkali metal hydrides or alkaline earth metal hydrides, metallic amides, such as alkali metal amides or alkaline earth metal amides, and alkoxides such as an alkali metal alkoxide or alkaline earth metal alkoxide. Preferably the base is an alkoxide such as an alkali metal alkoxide or alkaline earth metal alkoxide which typically is a C₁₋₄ alkoxide wherein the alkali metal is, e.g., lithium, sodium, or potassium, and the alkaline earth metal is, e.g., magnesium. In one embodiment the base is sodium methoxide. The base is typically employed in excess compared to the compound having the formula (2), e.g., in an amount of about 5 to about 15 mol base to 1 mol of the compound having the formula (2).

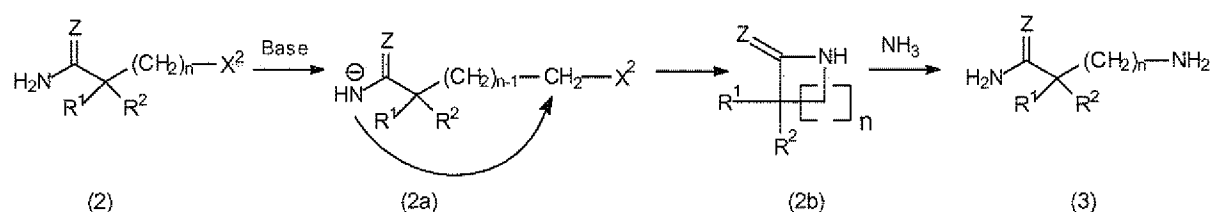
The reaction is typically conducted in a reaction medium such as water or an organic solvent. Typical organic solvents include tetrahydrofuran and C₁₋₄ alcohols (such as methanol, ethanol and propanol). More typical solvents are C₁₋₄ alcohols, with methanol being preferred.

The reaction temperature is not particularly limited and can range, e.g., from about 20 to about 100 °C, preferably from about 60 to about 90 °C.

The reaction pressure will depend on the reaction temperature and vice versa. The reaction will typically be conducted at a pressure of about 1 to about 20 bar, preferably about 3 to about 10 bar.

The reaction will be typically completed within about 1 to about 5 days depending on the specific conditions chosen.

Without wishing to be bound by theory it is assumed that the reaction proceeds via a lactam (2b). Because the γ -position is sterically crowded, an intramolecular attack by the possibly deprotonated amide functionality of (2a) seems to be more favorable than a substitution reaction with ammonia or the base. It is assumed that the lactam (2b) is opened by excess ammonia to give the compound having the formula (3).

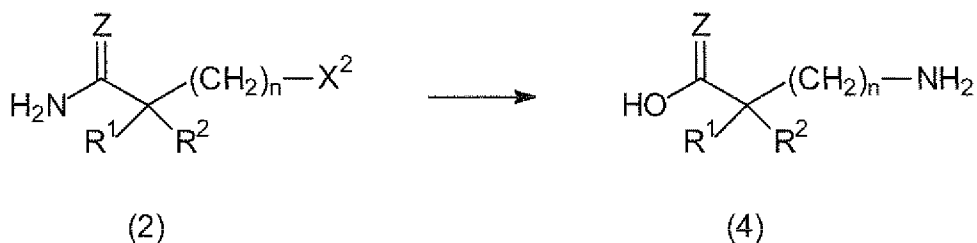


Scheme 7

The compound having the formula (3) can be isolated and/or purified, if necessary. Alternatively, it can be used in a subsequent reaction as such. Typical purification and isolation procedures include flash chromatography (e.g., using methylene chloride, methanol and concentrated aqueous ammonia), and crystallization (e.g., using ethyl acetate, a C_{1-4} alcohol such as ethanol or 2-propanol, or ethers such as 2-methyl-tetrahydrofuran).

Step C:

In step C a compound having the formula (2) is reacted with a metal hydroxide to form a compound having the formula (4).



Any metal hydroxide can be used as a base in the reaction of step C. Typical metals include alkali metals (such as lithium, sodium, and potassium) and alkaline earth metals (such as magnesium and calcium), more typically alkali metals. A preferred metal hydroxide is sodium hydroxide. The amount of metal hydroxide should be in excess of the amount of the compound having the formula (2). For example, amounts of more than 1 mol to about 5 mol metal hydroxide to 1 mol of the compound having the formula (2) can be employed.

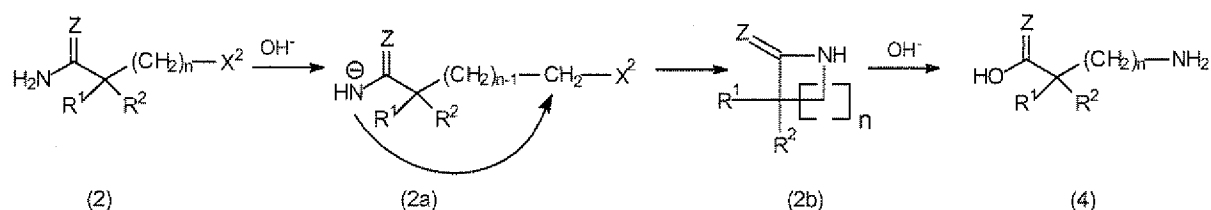
The use of the metal hydroxide ensures high yields and polymerization as an undesirable side reaction.

The reaction medium is not particularly limited. The solvent can typically be a C_{1-4} alcohol, such as methanol, ethanol, propanol, and butanol. A typical solvent is methanol.

The reaction temperature can be adjusted according to need. For illustration the reaction temperature can be in the range of about 20 to about 100 °C, such as about 50 to about 70 °C.

The duration of the reaction will depend on the conditions chosen but it will be typically complete within about a week.

Without wishing to be bound by theory it is assumed that the reaction proceeds via the same lactam (2b) as mentioned above in step B. Again it is assumed that an intramolecular attack by the activated amide functionality of (2a) is preferred compared to a substitution of X^2 with hydroxide. It is assumed that finally the lactam (2b) is opened by hydroxide to give the compound having the formula (4).



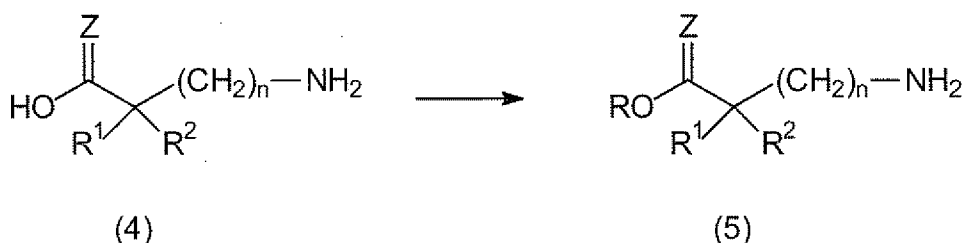
Scheme 8

In the process of the present invention the transformation of compound (2) to compound (4) occurs with high yield, e.g. almost quantitatively, and by-products resulting from side reactions, like polymerizations, are minimized by this step C.

The compound having the formula (4) can be isolated and/or purified, if desired or be used in a subsequent reaction *per se*. Typically precipitated metal- X^2 salt will be removed, e.g., by filtration or centrifugation, optionally followed by acidification of the reaction mixture to induce further precipitation. If desired, the resultant compound having the formula (4) can be further purified by crystallization and/or trituration.

Step D:

The compound having the formula (4) is reacted with an alcohol having the formula ROH, wherein R is a C_{1-4} alkyl group, to form a compound having the formula (5) in step D.



The reaction is not particularly limited and any suitable esterification reaction can be employed.

In one embodiment, the compound having the formula (4) can be activated by transformation into an acyl derivative (particularly an acyl chloride) prior to esterification. As appropriate chlorination agents, e.g., SOCl_2 , SO_2Cl_2 , PCl_3 , PCl_5 , POCl_3 and oxalyl chloride, particularly PCl_5 , can be mentioned. If desired, an acid (such as hydrochloric acid, sulfuric acid, phosphoric acid, acetic acid or trifluoroacetic acid, preferably hydrochloric acid) can be used in order to protect the amino function as the corresponding salt prior to chlorination.

In an alternative embodiment, the compound having the formula (4) is converted into the compound having the formula (5) without prior activation.

The esterification reaction is typically conducted in the alcohol ROH without a further solvent. Examples of the alcohol ROH include methanol, ethanol, propanol and butanol, whereby the alkyl group can be straight or branched. In one embodiment methanol is employed as an alcohol.

In order to promote the reaction an acid is typically employed. Examples of the acid include hydrochloric acid, sulfuric acid, phosphoric acid, acetic acid and trifluoroacetic acid, with hydrochloric acid being preferred.

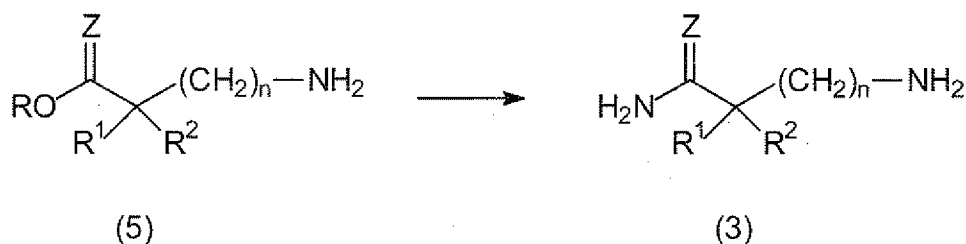
The reaction can be conducted at any suitable temperature and at any suitable pressure. For example, the temperature can be in the range of about 0 to about 60 °C, preferably about 10 to about 40 °C. In one embodiment ambient pressure is employed.

The reaction will usually be complete within about 10 to 20 hours.

The compound having the formula (5) can be used *per se* in a subsequent reaction step. Alternatively it can be isolated and/or purified beforehand.

Step E:

In step E the compound having the formula (5) is reacted with ammonia to form a compound having the formula (3):



The reaction of step E is known in the art and is, e.g., described in AT-A-502 804. The reaction can be conducted using ammonia in gaseous form or in the form of an aqueous or alcoholic solution.

The reaction can be conducted in a C₁₋₆ alcohol, such as methanol, as a reaction medium.

Typical reaction temperatures range from about 10 to about 200 °C, preferably from about 50 to about 180 °C, more preferably from about 80 to about 120 °C.

The reaction pressure will usually be in the range from about 1 to about 50 bar, preferably from about 2 to about 40 bar, more preferably from about 5 to about 30 bar.

If desired, 0 to about 200 mol-% of an alkali metal C₁₋₆ alcoholate may be added based on the compound having the formula (5). Examples of possible alkali metals include lithium, sodium and potassium. A preferred amount of alcoholate is from about 1 to about 100 mol-%, more preferably from about 10 to about 30 mol-%. If the alcoholate is added, it is preferable to neutralize excess alcoholate before the compound having the formula (3) is isolated. This can be done, for example, by adding a slightly acidic compound, such as a protic acid with a pK_a from 2 to 14, more preferably from 4 to 10, such as ammonium chloride, e.g., in an amount of about 100 to about 200 mol-% based on the compound having the formula (5). However, in a preferred embodiment, Step E is carried out without alcoholate addition and subsequent neutralization.

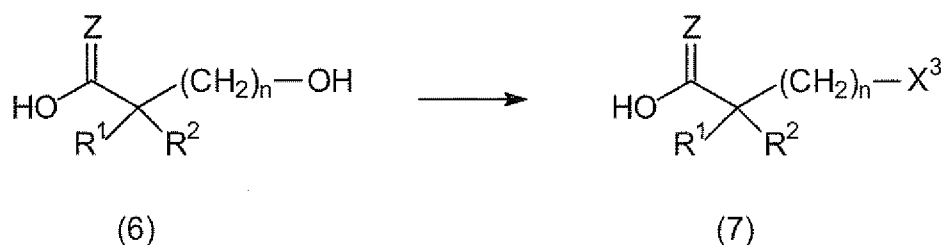
Further details on step E can be found in AT-A-502 804.

The compound having the formula (3) can be isolated and/or purified according to known procedures, such as extraction, distillation or combinations thereof.

In the preceding description steps D and E are described as individual reaction steps. However, it is not necessary to conduct them separately. Rather steps D and E can be conducted in a one-pot reaction.

Step F:

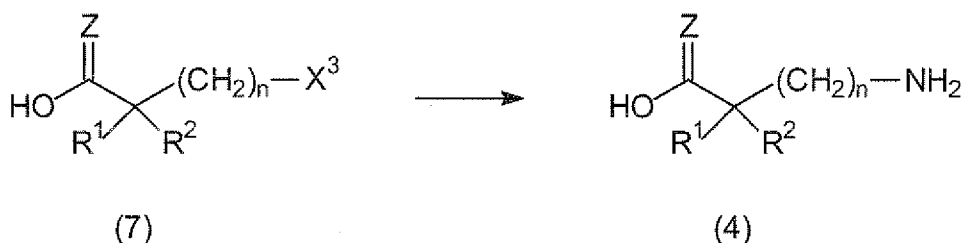
The compound having the formula (7) can be prepared by treating a compound having the formula (6) with an aqueous acid HX^3 (step F):



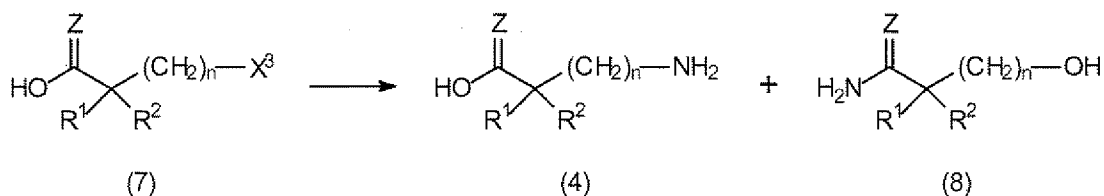
This step has been described, e.g., in *J. Am. Chem. Soc.* **155**, 77, 3016–3018. In this reference hydroxypivalic acid is heated in aqueous hydrobromic acid to yield the compound (7'). This method can be adapted in order to provide the other compounds having the formula (7).

Step G:

The compound having the formula (7) can be transformed into the compound having the formula (4) by reaction with ammonia (step G):



In this reaction typically a mixture of the desired compound having the formula (4) and an undesired by-product (8) is formed.



Scheme 9

The compounds having the formulae (4) and (8) can be separated by any suitable technique. One possibility is to exploit the different solubility of the compounds having the formulae (4) and (8) in a solvent, e.g., in methylene chloride. In order to separate the compounds having the formula (4) and (8), the mixture is contacted with the solvent (e.g., methylene chloride) until one of the compounds is substantially dissolved, while the other compound remains substantially undissolved. Within the present invention "substantially dissolved" means that at least 95 wt.-% of the total amount of a compound is dissolved in the solvent. Within the present invention "substantially undissolved" means that at most 30 wt.-% of the total amount of a compound is dissolved in the solvent. The compound that remains substantially undissolved can be subsequently separated from the solution of the compound that has been substantially dissolved by solid-liquid separation, such as filtration, centrifugation or the like.

The contacting temperature will vary depending on the specific compounds having the formulae (4) and (8) as well as on the solvent. It can be, e.g., in the range of about 20 to about 40 °C. The duration of the contacting step should be chosen appropriately depending on the solubility and can be, for example, about 1 to about 5 hours. The insoluble compound can be separated from the suspension as a solid by any suitable technique, such as filtration, centrifugation, or the like. The soluble compound can be obtained from the remaining solution, e.g., by extraction, evaporation, and the like, if desired.

In one example, the solvent is methylene chloride. In this embodiment the mixture of the compounds having the formulae (4) and (8) is contacted with methylene chloride for an appropriate amount of time (e.g., about 1 to about 5 hours) and at an appropriate temperature (e.g., about 20 to about 40 °C). The compound having the formula (8) is dissolved under these conditions, so that it is possible to obtain the compound having the formula (4) by separating the solid from the liquid. This embodiment is preferred in present step G. However, the present invention is not restricted to methylene chloride or these conditions.

If desired, the compound having the formula (4) can be further purified by known procedures, such as recrystallization.

The ammonia can be supplied in gaseous form or in solution. For example, the ammonia can be employed in an amount of about 1 to about 100 mol, preferably about 10 to about 70 mol, most preferably 40 mol per 1 mol the compound having the formula (7).

The reaction will typically be conducted in an organic solvent. Examples of suitable solvents include halogenated C₁₋₄ hydrocarbons (such as methylene chloride), C₁₋₄ alcohols (such as methanol, ethanol, propanol and butanol), hydrocarbons (such as toluene) and ethers (such as dioxane).

The reaction temperature is not particularly limited and can be in the range of about 0 to about 100 °C. The reaction pressure will be usually in the range of about 1 to about 10 bar.

Although the reaction is not particularly limited because it is possible to separate the compound having the formula (4) from the compound having the formula (8), it is preferred to select reaction conditions in which the ratio of the compound having the formula (4) to the compound having the formula (8) is high (e.g., more than 1:1). The present inventors have surprisingly found that the ratio between the compound having the formula (4) and the compound having the formula (8) can be adjusted by suitably selecting the reaction conditions, in particular by choosing a suitable solvent. While the ratio of (4) : (8) is 0.85 : 1 if methanol is used as solvent, the ratio of (4) : (8) is improved to more than 2.2 : 1 if a solvent having a lower polarity is employed. Preferred solvents for this step are thus nonpolar, aprotic solvents having a relative static permittivity at 20°C of below 15, more preferably below 10, such as below 8. Preferred examples of suitable nonpolar, aprotic solvents include hydrocarbons (such as toluene) and ethers (such as dioxane).

If a solvent having a lower polarity (such as an ether like dioxane) is used, the reaction temperature is preferably in the range of about 20 to about 70 °C, more preferably about 50 to about 70 °C. The pressure is preferably in the range of about 1 to about 10 bar, preferably about 3 to about 5 bar. In one option of this embodiment, the ammonia is employed in solution, typically in an amount of about 1 to about 100 mol, preferably about 10 to about 70 mol, most preferably about 30 to about 50 mol per 1 mol the compound having the formula (7).

In an alternative option of this embodiment, gaseous ammonia can be passed through the reaction medium including a solvent having a lower polarity (such as an ether like dioxane). In this case the reaction temperature is preferably in the range of about 10 to about 40 °C, more preferably about 20 to about 30 °C. Ammonia is typically used in molar excess and the amount of ammonium is typically from about 1 to about 100 mol, preferably about 1.1 to about 50 mol, per 1 mol the compound having the formula (7). The duration of the reaction will depend on the reaction conditions and will typically be from about 2 to about 12 hours, e.g., from about 6 to about 7 hours.

In the present application each step (A), (B), (C), (D), (E), (F) or (G) can be conducted alone. In addition, at least the following combinations of steps are envisaged:

(A) + (B); (A) + (C); (A) + (C) + (D); (A) + (C) + (D) + (E); (C) + (D); (C) + (D) + (E); (D) + (E); (F) + (G); (F) + (G) + (D); (F) + (G) + (D) + (E); (G) + (D); and (G) + (D) + (E).

It is understood that each preferred and more preferred embodiment of each reaction step is preferred or more preferred not only for the individual reaction steps but also for all of the above mentioned combinations of steps.

The present invention provides a simple and convenient method for preparing an ω -amino-alkane(thio)amide having the formula (3) which is suitable for production on an industrial scale. The purity of the obtained ω -amino-alkane(thio)amide having the formula (3) is high, so that it can be employed in the preparation of pharmaceuticals such as aliskiren. The method is particularly advantageous because the reaction times are short and the yields are high. Because the intermediate having the formula (5) does not need to be isolated a further reduction of time and costs is achieved.

The following examples describe the present invention in detail, but they are not to be construed to be in any way limiting for the present invention.

EXAMPLES

Example 1 (Step A)

Chloro pivalic acid chloride (1') (52.0 mL, 402.5 mmol) was dissolved in methylene chloride (50 mL) at room temperature. This solution was added to a saturated solution of ammonia in

methylene chloride (1000 mL) over 5 min while keeping the temperature below 20 °C. A stream of ammonia was passed through the ice-cold solution for 100 min, then stirring was continued for further 60 min. The resulting suspension was quenched with water (250 mL) in order to dissolve precipitated ammonium chloride. The layers were separated and the organic layer was washed with water (250 mL). Then the combined aqueous layers were back-extracted with methylene chloride (150 mL). The combined organic layers were reduced to 40-50% of their weight by evaporation under reduced pressure. Subsequently, the solution was cooled to 3 °C and treated with n-hexane (2.0 L) which was added dropwise over a period of 20-30 min. The resulting suspension was allowed to stir for further 30-40 min. Finally, the resulting solid was isolated by filtration over a G3 sintered funnel, washed with n-hexane (100 ml) and subsequently dried at room temperature under reduced pressure. Chloro pivalic amide (2') was obtained as a solid in 69% yield (37.75 g, 278.4 mmol).

¹H-NMR (300 MHz): δ = 1.32 (s, 6H, CH₃), 3.61 (s, 2H, CH₂), 5.77 (br s, 2H, NH₂) ppm.

Example 2 (Step B)

Chloro pivalic amide (2') (5.0 g, 36.7 mmol) was placed in an autoclave and mixed with a solution of ammonia in methanol (2.4 M, 157 mL, 377 mmol) and a solution of sodium methoxide in methanol (30%, 70 mL, 367 mmol). The autoclave was closed and the mixture was heated to 60 °C for 50 h. The mixture was cooled to room temperature, the overpressure was released and the suspension was filtered. The basic filtrate was neutralized (pH 7) by dropwise addition of HCl at 2-5 °C, and the resulting solid was removed by filtration. The filtrate was evaporated under reduced pressure and the crude product was purified by flash chromatography on silica gel (eluent: CH₂Cl₂ / MeOH / conc. aq. NH₃ : 70 / 30 / 1.5). The resulting solid was then crystallized from ethyl acetate to give 3-amino-2,2-dimethyl propionamide (3') in 61% yield (2.58 g, 22.2 mmol). Alternatively, the crude product was directly re-crystallized from refluxing 2-propanol to yield 3-amino-2,2-dimethyl propionamide (3') in 62% yield (2.63 g, 22.6 mmol).

¹H-NMR (300 MHz, DMSO-d₆): δ = 1.02 (s, 6H, CH₃), 1.33 (br s, 2H, NH₂), 2.56 (s, 2H, CH₂) ppm.

¹³C-NMR (75 MHz, DMSO-d₆): δ = 23.0 (CH₃), 42.6 (C_q), 50.6 (CH₂), 178.7 (CONH₂) ppm.

Example 3 (Step C)

Chloro pivalic amide (2') (15 g, 110.6 mmol) was mixed with sodium hydroxide (13.27 g, 0.332 mol) in methanol. The suspension was stirred at room temperature until it turned into a clear solution. The solution was heated to 50-53 °C for 70 h without stirring while the reaction vessel was closed. Subsequently, the resulting suspension was stirred for 30 min at 2 °C, the precipitate (mainly NaCl) was filtered off and washed with methanol (3 x 5 mL). The filtrate was cooled to 2 °C and conc. aqueous HCl (18 mL) was added dropwise, whereby the temperature did not exceed 20 °C. The resulting suspension was allowed to stir for further 10 min at 0 °C. The precipitate (mainly NaCl) was filtered off and washed with methanol (3 x 20 mL). The filtrate was evaporated under reduced pressure, the remaining residue was mixed with 2-propanol and the resulting suspension was stirred for 60 min at 2 °C. The solid was filtered off and washed with ice-cold 2-propanol (2 x 5 mL). The solid was dried under reduced pressure at room temperature over P₄O₁₀. Amino acid (4') was isolated in a yield of 69%. (8.92 g, 76.1 mmol).

¹H-NMR (300 MHz, CD₃OD / D₂O): δ = 1.14 (s, 6H, CH₃), 2.95 (s, 2H, CH₂) ppm.

¹³C-NMR (75 MHz, CD₃OD / D₂O): δ = 24.3 (CH₃), 42.1 (C_q), 48.6 (CH₂), 184.8 (COOH) ppm.

Example 4 (Step D)

Amino acid (4') (11.7 g, 99.9 mmol) was treated with a solution of hydrogen chloride in methanol (13.5%, 117 mL, 446 mmol) at room temperature and the mixture was left to stir for 20 h at room temperature. The volatiles were removed under reduced pressure to give methyl ester (5') as a solid in a yield of 99% (16.57 g, 98.84 mmol).

¹H-NMR (300 MHz, CD₃OD): δ = 1.24 (s, 6H, CH₃), 3.09 (s, 2H, CH₂), 3.65 (s, 3H, OCH₃) ppm.

¹³C-NMR (75 MHz, CD₃OD): δ = 23.5 (CH₃), 42.1 (C_q), 47.4 (CH₂), 53.9 (OCH₃), 178.6 (COOR) ppm.

Example 5 (Step E)

Methyl ester (5') (12.42 g, 74.09 mmol) was mixed with a solution of ammonia in methanol (22%, 120 mL, 1.55 mol) at room temperature. The resulting solution was placed in an autoclave which was charged with additional gaseous ammonia. The mixture was heated to 60 °C and allowed to stir for 2 days at a pressure of 5 bar. The mixture was cooled to room temperature and the excess ammonia was released. The solvent was removed under reduced pressure to give 3-amino-2,2-dimethyl-propionamide (3') as a solid in quantitative yield (10.94 g).

$^1\text{H-NMR}$ (300 MHz, DMSO-d_6): δ = 1.02 (s, 6H, CH_3), 1.33 (br s, 2H, NH_2), 2.56 (s, 2H, CH_2) ppm.

$^{13}\text{C-NMR}$ (75 MHz, DMSO-d_6): δ = 23.0 (CH_3), 42.6 (C_q), 50.6 (CH_2), 178.7 (CONH_2) ppm.

Example 6 (Step F)

Hydroxy pivalic acid (6') (18.0 g, 152.4 mmol) was mixed with aqueous HBr (62%, 100 mL). The mixture was heated to 100 °C and the temperature was kept for 19 h. The mixture was cooled to ambient temperature and diluted with 250 mL of water. The aqueous layer was extracted with diethyl ether (2 x 50 mL). The combined organic extracts were washed with water (3 x 25 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure to provide an oil which crystallized on standing. Bromo pivalic acid (7') was obtained in a yield of 66% (18.26 g, 100.9 mmol).

$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ = 1.34 (s, 6H, CH_3), 1.99 (s, 2H, CH_2) ppm.

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ = 24.3 (CH_3), 40.8 (CH_2), 44.2 (C_q), 181.5 (COOH) ppm.

Example 7 (Step G)

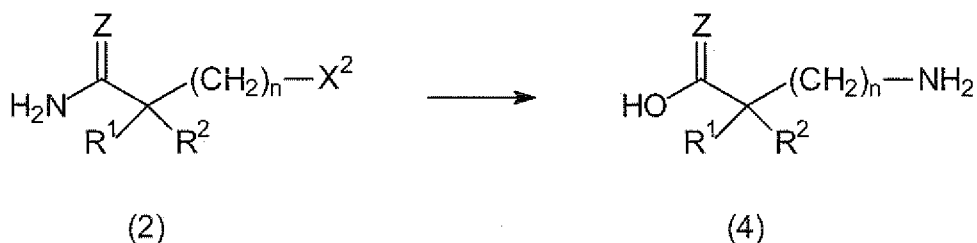
Bromo pivalic acid (7') (20.0 g, 110.5 mmol) was dissolved in dioxane (20 mL). The resulting solution was placed in an autoclave, which was subsequently charged with ammonia. The reaction mixture was heated to 60 °C and allowed to stir for 16 h at a pressure of 3 bar. Subsequently, the mixture was cooled to room temperature and the excess ammonia was released. The suspension was filtered over a G3 sintered funnel and the resulting solid was washed with dioxane. This solid was suspended in methylene chloride (10 mL) and the suspension was refluxed for 2 h. After cooling to room temperature the suspension was filtered, the resulting solid was washed with ice-cold methylene chloride (2 x 5 mL) and dried overnight under reduced pressure (< 50 mbar, 40 °C) to give amino pivalic acid (4') in a yield of 54% (6.99 g, 59.67 mmol).

$^1\text{H-NMR}$ (300 MHz, $\text{CD}_3\text{OD} / \text{D}_2\text{O}$): δ = 1.14 (s, 6H, CH_3), 2.95 (s, 2H, CH_2) ppm.

$^{13}\text{C-NMR}$ (75 MHz, $\text{CD}_3\text{OD} / \text{D}_2\text{O}$): δ = 24.3 (CH_3), 42.1 (C_q), 48.6 (CH_2), 184.8 (COOH) ppm.

CLAIMS

1. A method for the preparation of an ω -amino-alkaneamide or an ω -amino-alkanethioamide having the formula (3), the method comprising the steps of:
 - (i) reacting a compound having the formula (2) with a metal hydroxide to form a compound having the formula (4) (step C):



wherein

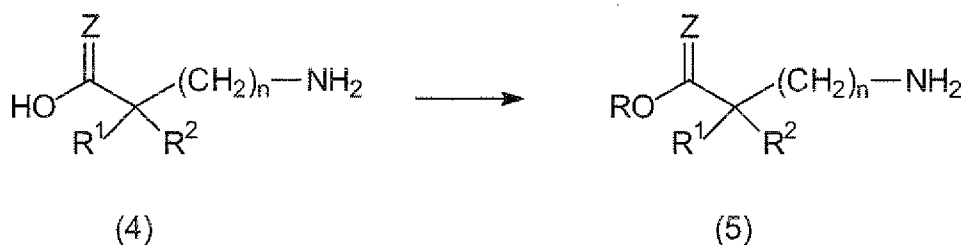
Z is O or S;

R¹ and R² are independently selected from the group consisting of H and C₁₋₈ alkyl, wherein at most one of R¹ and R² is H;

n is an integer from 1 to 5; and

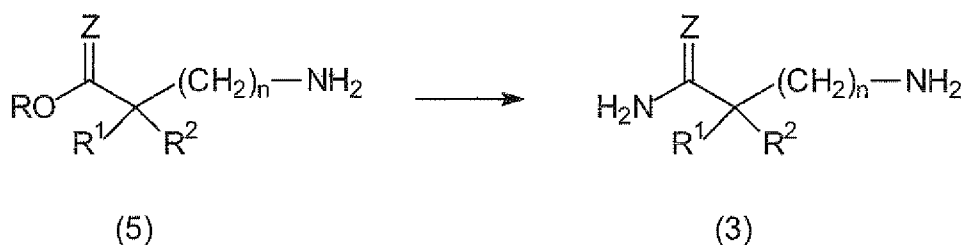
X² is a leaving group;

- (ii) reacting the compound having the formula (4) with an alcohol having the formula ROH, wherein R is a C₁₋₄ alkyl group, to form a compound having the formula (5) (step D):



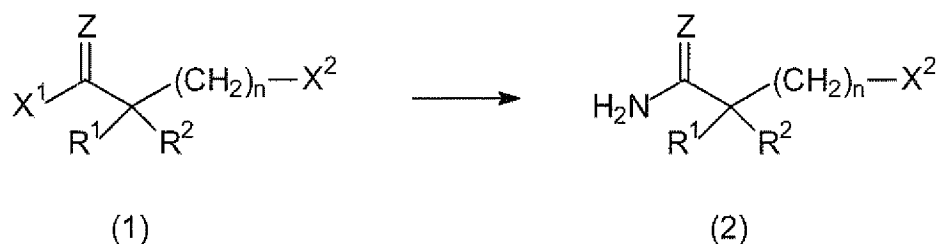
wherein Z, R¹, R², and n are as defined above; and

- (iii) reacting the compound having the formula (5) with ammonia to form a compound having the formula (3) (step E):



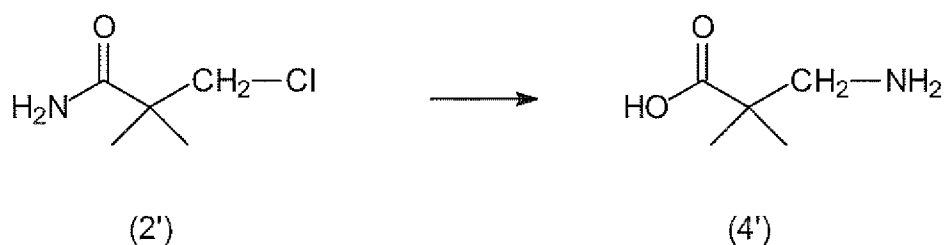
wherein R, Z, R¹, R², and n are as defined above.

2. The method of claim 1 wherein the compound having the formula (2) is prepared by reacting a compound having the formula (1) with ammonia to form a compound having the formula (2) (step A):

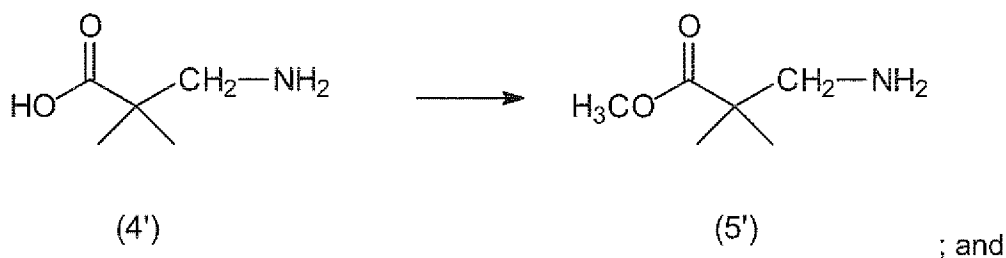


wherein Z, R¹, R², X² and n are as defined in claim 1 and X¹ is selected from the group consisting of halogen and R'-C(O)-O-, wherein R' is a C₁₋₈ alkyl group.

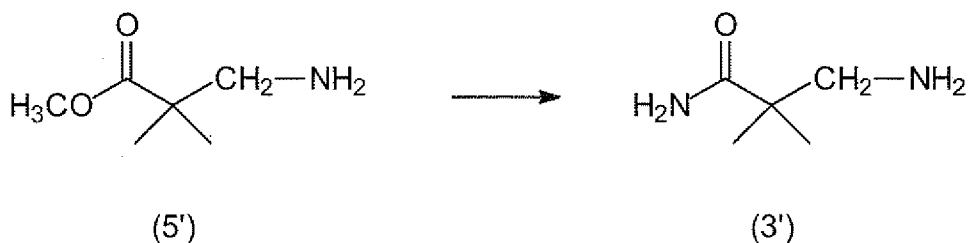
3. A method for the preparation of an ω-amino-alkaneamide or an ω-amino-alkanethioamide having the formula (3'), the method comprising the steps of:
- (i) reacting a compound having the formula (2') with a metal hydroxide to form a compound having the formula (4') (step C):



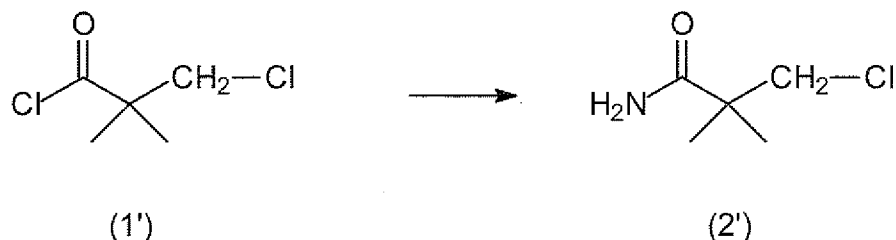
- (ii) reacting the compound having the formula (4') with methanol to form a compound having the formula (5') (step D):



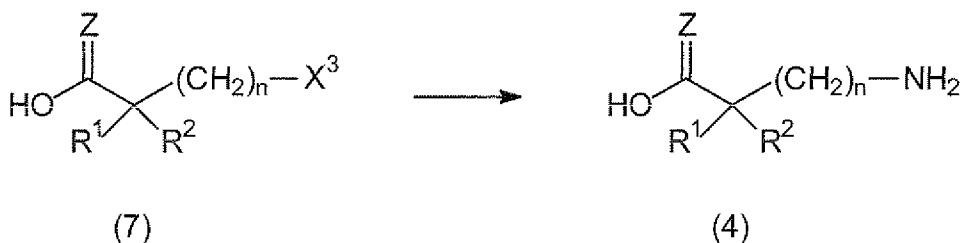
- (iii) reacting the compound having the formula (5') with ammonia to form a compound having the formula (3') (step E):



4. The method of claim 3 wherein the compound having the formula (2') is prepared by reacting a compound having the formula (1') with ammonia to form the compound having the formula (2') (step A'):



5. A method for the preparation of an ω -amino-alkaneamide or an ω -amino-alkanethioamide having the formula (3), the method comprising the steps of:
- (i) reacting a compound having the formula (7) with ammonia to form a compound having the formula (4) (step G):



wherein

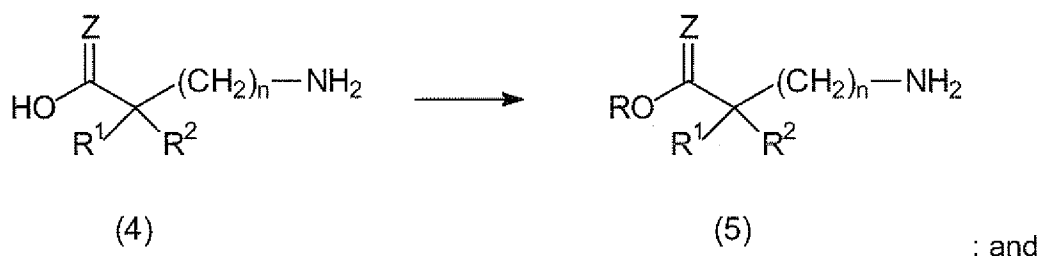
Z is O or S;

R^1 and R^2 are independently selected from the group consisting of H and C_{1-8} alkyl, wherein at most one of R^1 and R^2 is H;

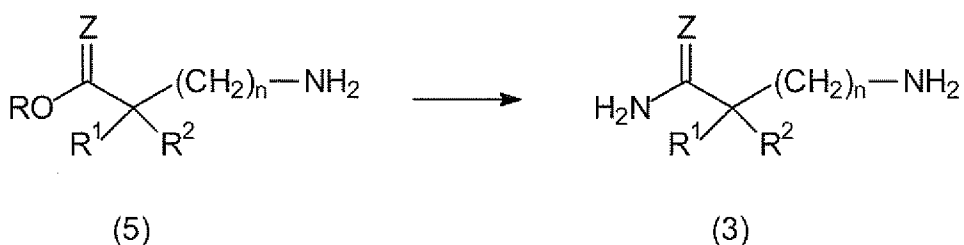
n is an integer from 1 to 5; and

X^3 is a leaving group;

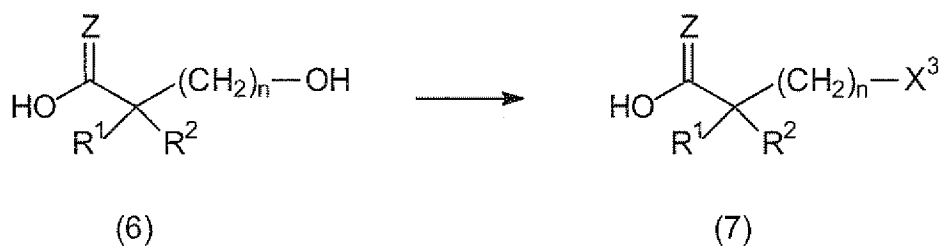
- (ii) reacting the compound having the formula (4) with an alcohol having the formula ROH , wherein R is a C_{1-4} alkyl group, to form a compound having the formula (5) (step D):



- (iii) reacting the compound having the formula (5) with ammonia to form the compound having the formula (3) (step E):



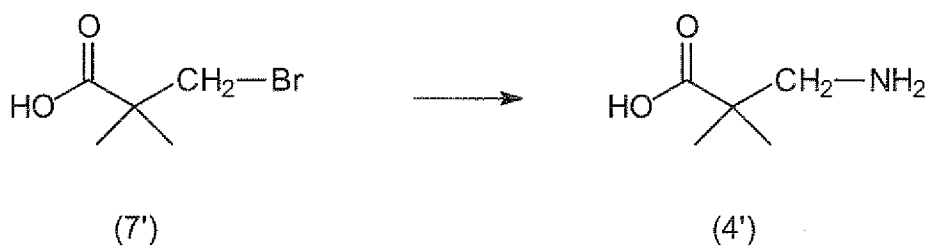
6. The method of claim 5, wherein the compound having the formula (7) is prepared by treating a compound having the formula (6) with an aqueous acid HX^3 (step F):



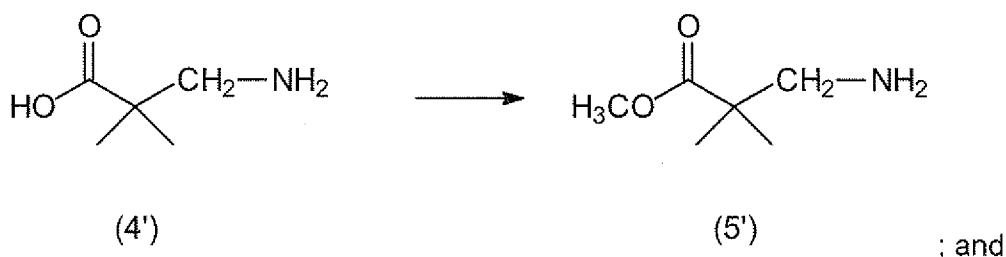
wherein Z, R^1 , R^2 , n and X^3 are as defined in claim 5.

7. A method for the preparation of an ω -amino-alkaneamide or an ω -amino-alkanethioamide having the formula (3'), the method comprising the steps of:

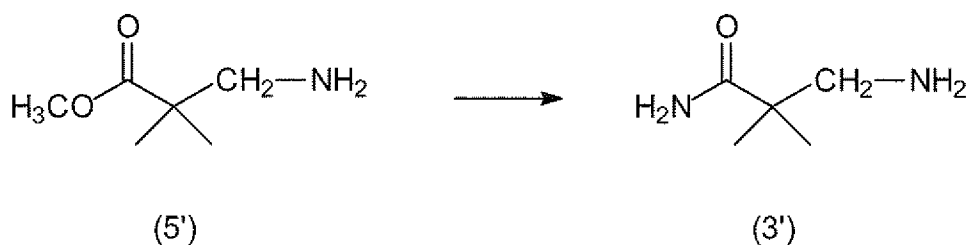
- (i) reacting a compound having the formula (7') with ammonia to form a compound having the formula (4') (step G'):



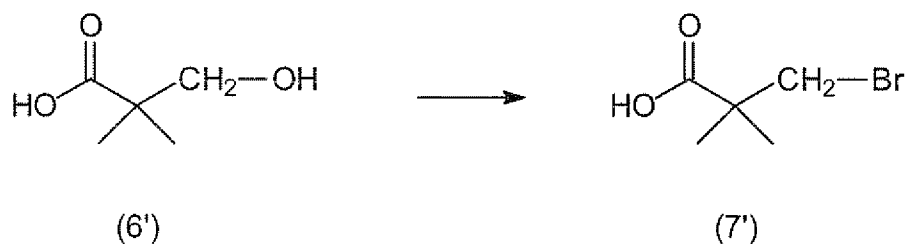
- (ii) reacting the compound having the formula (4') with methanol to form a compound having the formula (5') (step D'):



- (iii) reacting the compound having the formula (5') with ammonia to form the compound having the formula (3') (step E'):

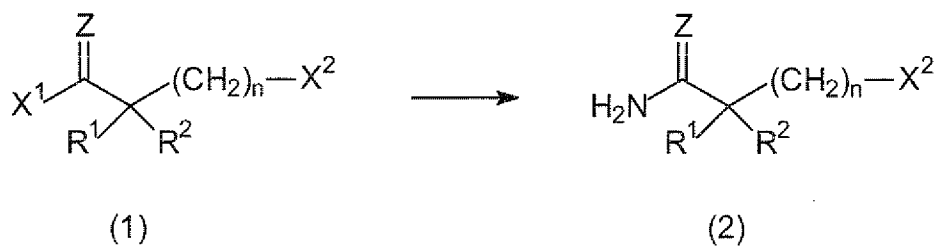


8. The method of claim 7, wherein the compound having the formula (7') is prepared by treating a compound having the formula (6') with an aqueous HBr (step F'):



9. A method for the preparation of an ω -amino-alkaneamide or an ω -amino-alkanethioamide having the formula (3), the method comprising the steps of:

- (i) reacting a compound having the formula (1) with ammonia to form a compound having the formula (2) (step A):



wherein

X^1 is selected from the group consisting of halogen and $\text{R}'-\text{C}(\text{O})-\text{O}-$, wherein R' is a C_{1-8} alkyl group;

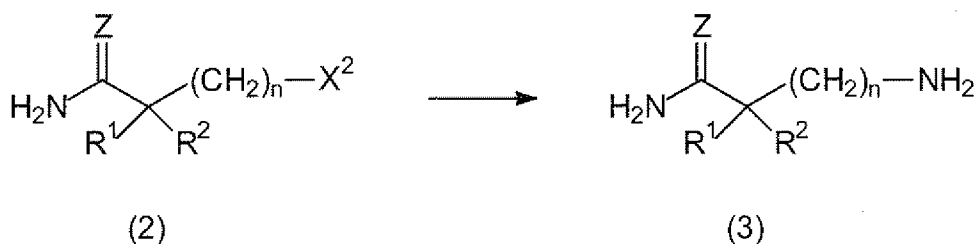
Z is O or S;

R^1 and R^2 are independently selected from the group consisting of H and C_{1-8} alkyl, wherein at most one of R^1 and R^2 is H;

n is an integer from 1 to 5; and

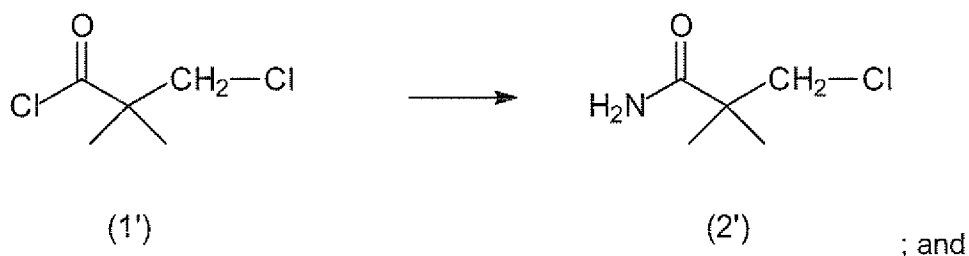
X^2 is a leaving group; and

- (ii) reacting the compound having the formula (2) with ammonia and a base to form the compound having the formula (3) (step B):



10. A method for the preparation of an ω -amino-alkaneamide or an ω -amino-alkanethioamide having the formula (3'), the method comprising the steps of:

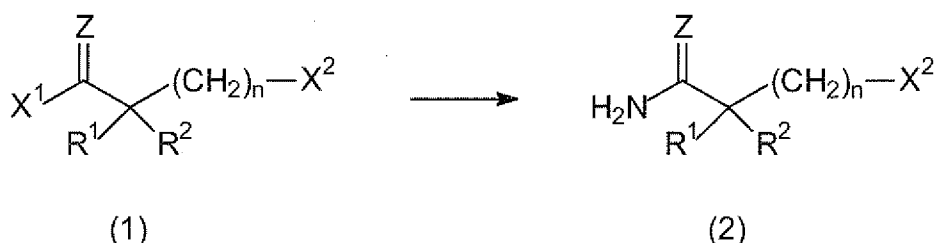
- (i) reacting a compound having the formula (1') with ammonia to form a compound having the formula (2') (step A):



- (ii) reacting the compound having the formula (2') with ammonia and a base to form the compound having the formula (3') (step B):



11. A method for preparing a compound having the formula (2) which comprises reacting a compound having the formula (1) with ammonia in a homogeneous reaction medium to form the compound having the formula (2) (step A):



wherein

X^1 is selected from the group consisting of halogen and $\text{R}'\text{-C(O)-O-}$, wherein R' is a C_{1-8} alkyl group;

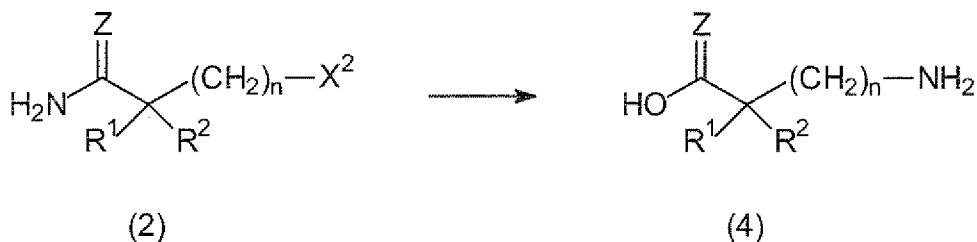
Z is O or S;

R^1 and R^2 are independently selected from the group consisting of H and C_{1-8} alkyl, wherein at most one of R^1 and R^2 is H;

n is an integer from 1 to 5; and

X^2 is a leaving group.

12. A method for preparing a compound having the formula (4) which comprises reacting a compound having the formula (2) with a metal hydroxide to form the compound having the formula (4) (step C):



wherein

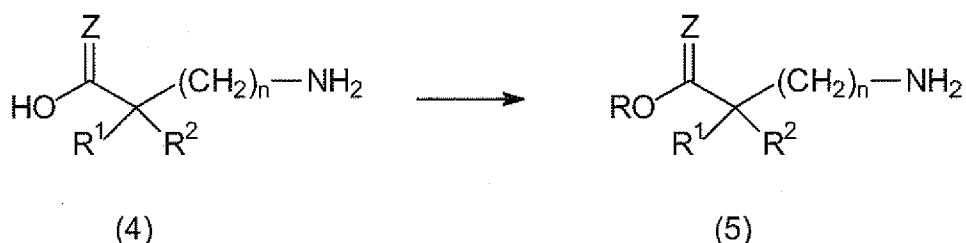
Z is O or S;

R^1 and R^2 are independently selected from the group consisting of H and C_{1-8} alkyl, wherein at most one of R^1 and R^2 is H;

n is an integer from 1 to 5; and

X^2 is a leaving group.

13. A method for preparing a compound having the formula (5) which comprises reacting a compound having the formula (4) with an alcohol having the formula ROH , wherein R is a C_{1-4} alkyl group, to form the compound having the formula (5) (step D):



wherein

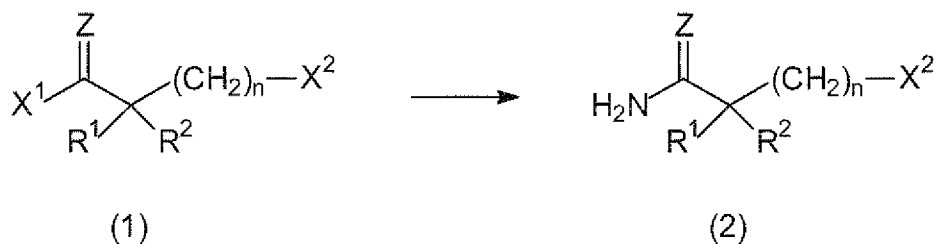
Z is O or S;

R¹ and R² are independently selected from the group consisting of H and C₁₋₈ alkyl, wherein at most one of R¹ and R² is H;

n is an integer from 1 to 5.

14. A method for preparing a compound having the formula (4), the method comprising the steps of:

- (i) reacting a compound having the formula (1) with ammonia to form a compound having the formula (2) (step A):



wherein

X¹ is selected from the group consisting of halogen and R'-C(O)-O-, wherein R' is a C₁₋₈ alkyl group;

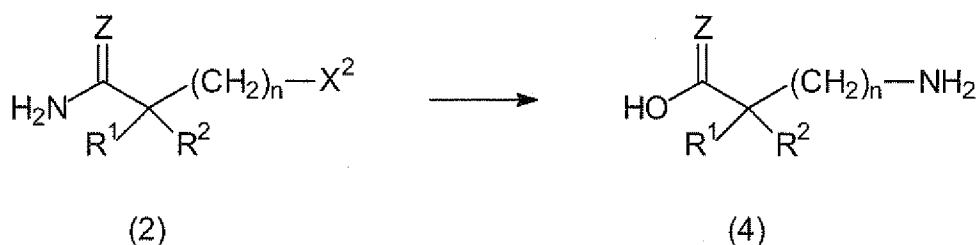
Z is O or S;

R¹ and R² are independently selected from the group consisting of H and C₁₋₈ alkyl, wherein at most one of R¹ and R² is H;

n is an integer from 1 to 5; and

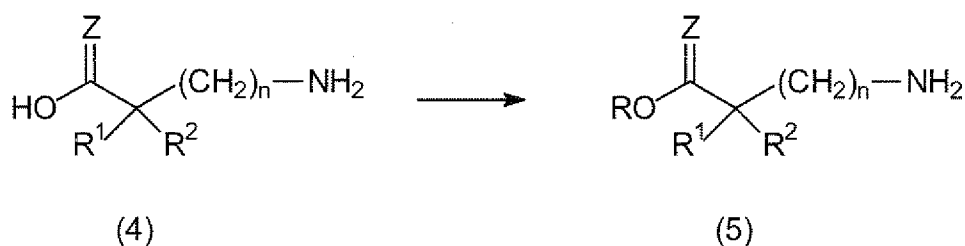
X² is a leaving group; and

- (ii) reacting the compound having the formula (2) with a metal hydroxide to form the compound having the formula (4) (step C):



15. A method for preparing a compound having the formula (3), the method comprising the steps of:

- (i) reacting a compound having the formula (4) with an alcohol having the formula ROH, wherein R is a C₁₋₄ alkyl group, to form a compound having the formula (5) (step D):



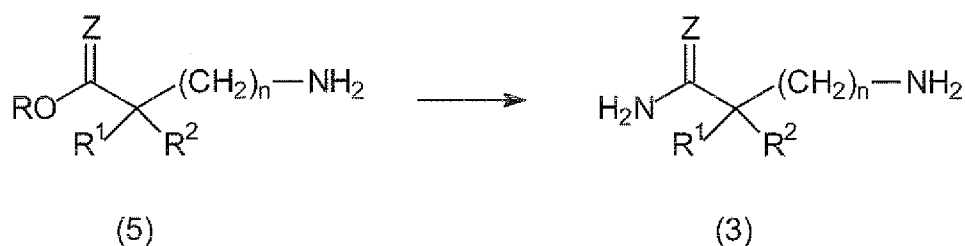
wherein

Z is O or S;

R¹ and R² are independently selected from the group consisting of H and C₁₋₈ alkyl, wherein at most one of R¹ and R² is H;

n is an integer from 1 to 5; and

- (ii) reacting the compound having the formula (5) with ammonia to form the compound having the formula (3) (step E):



16. A method for preparing a compound having the formula (4) which comprises reacting a compound having the formula (7) with ammonia to form the compound having the formula (4) (step G):



wherein

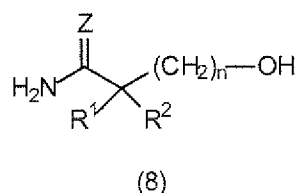
Z is O or S;

R¹ and R² are independently selected from the group consisting of H and C₁₋₈ alkyl, wherein at most one of R¹ and R² is H;

n is an integer from 1 to 5; and

X³ is a leaving group.

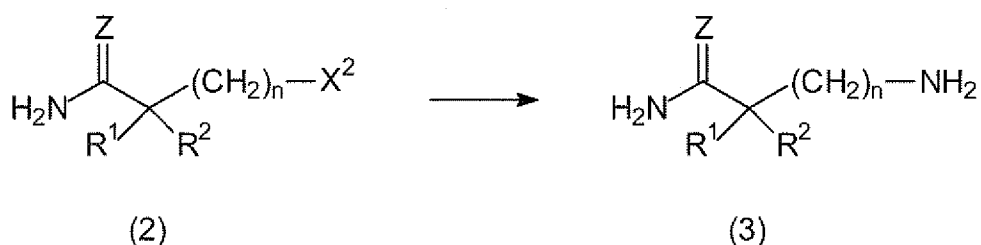
17. The method of claim 16, wherein the reaction is conducted in a reaction solvent having a relative static permittivity at 20°C of below about 15, preferably a hydrocarbon (such as toluene) or an ether (such as dioxane).
18. The method of claim 16 or 17, wherein a mixture of the compound having the formula (4) and of a compound having the formula (8) is obtained in step G



wherein Z, R¹, R² and n are as defined in claim 16,

and wherein the mixture of the compounds having the formulae (4) and (8) is contacted with a solvent, in which the compound having the formula (4) is substantially insoluble under the contacting conditions and in which the compound having the formula (8) is substantially soluble under the contacting conditions (preferably methylene chloride), in order to substantially dissolve the compound having the formula (8) and wherein the compound having the formula (4) is subsequently separated from the solution of the compound having the formula (8) by solid-liquid separation.

19. A method for preparing a compound having the formula (3) which comprises reacting a compound having the formula (2) with ammonia and a base to form the compound having the formula (3) (step B):



wherein

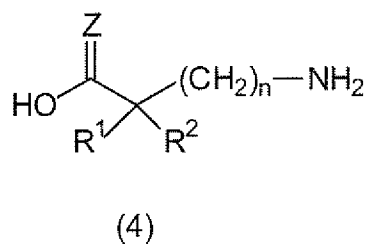
Z is O or S;

R¹ and R² are independently selected from the group consisting of H and C₁₋₈ alkyl, wherein at most one of R¹ and R² is H;

n is an integer from 1 to 5; and

X² is a leaving group.

20. A compound having the formula (4):



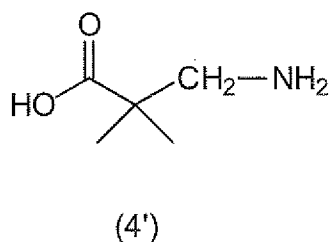
wherein

Z is O or S;

R¹ and R² are independently selected from the group consisting of H and C₁₋₈ alkyl, wherein at most one of R¹ and R² is H;

n is an integer from 1 to 5;

preferably wherein the compound has the formula (4'):



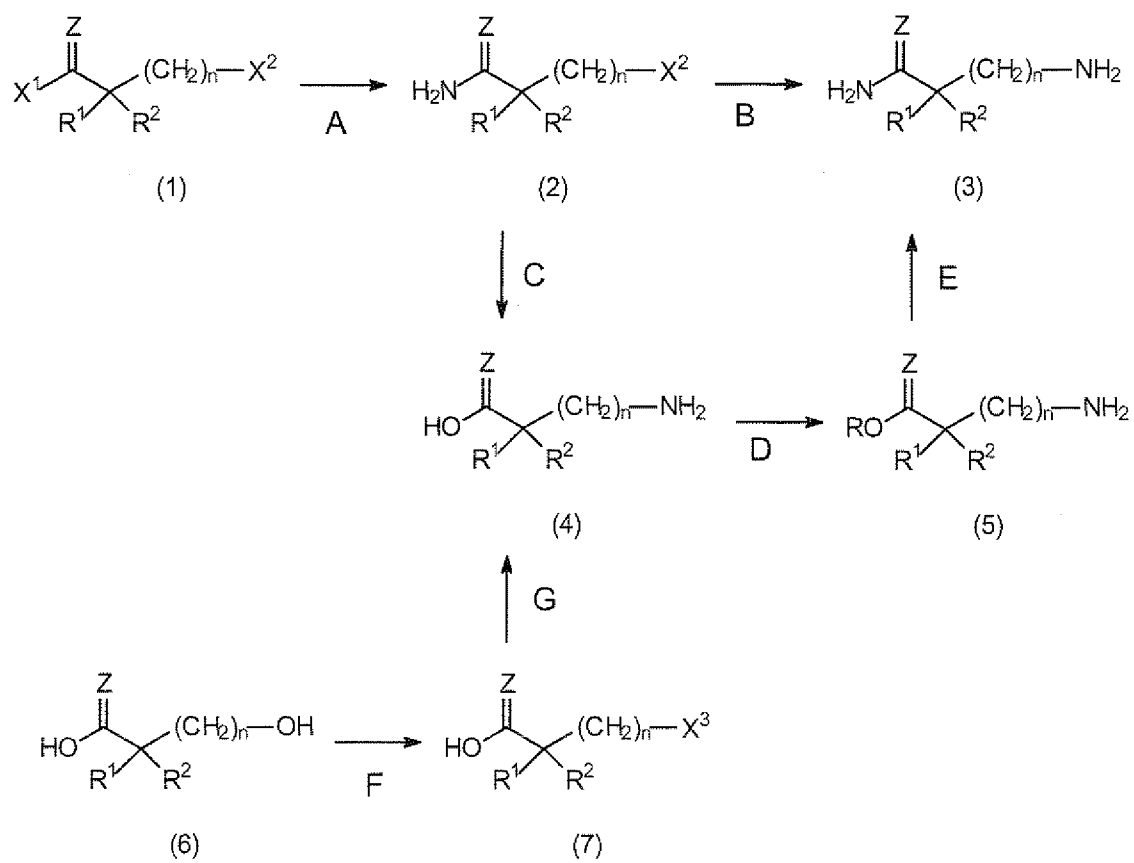


Figure 1

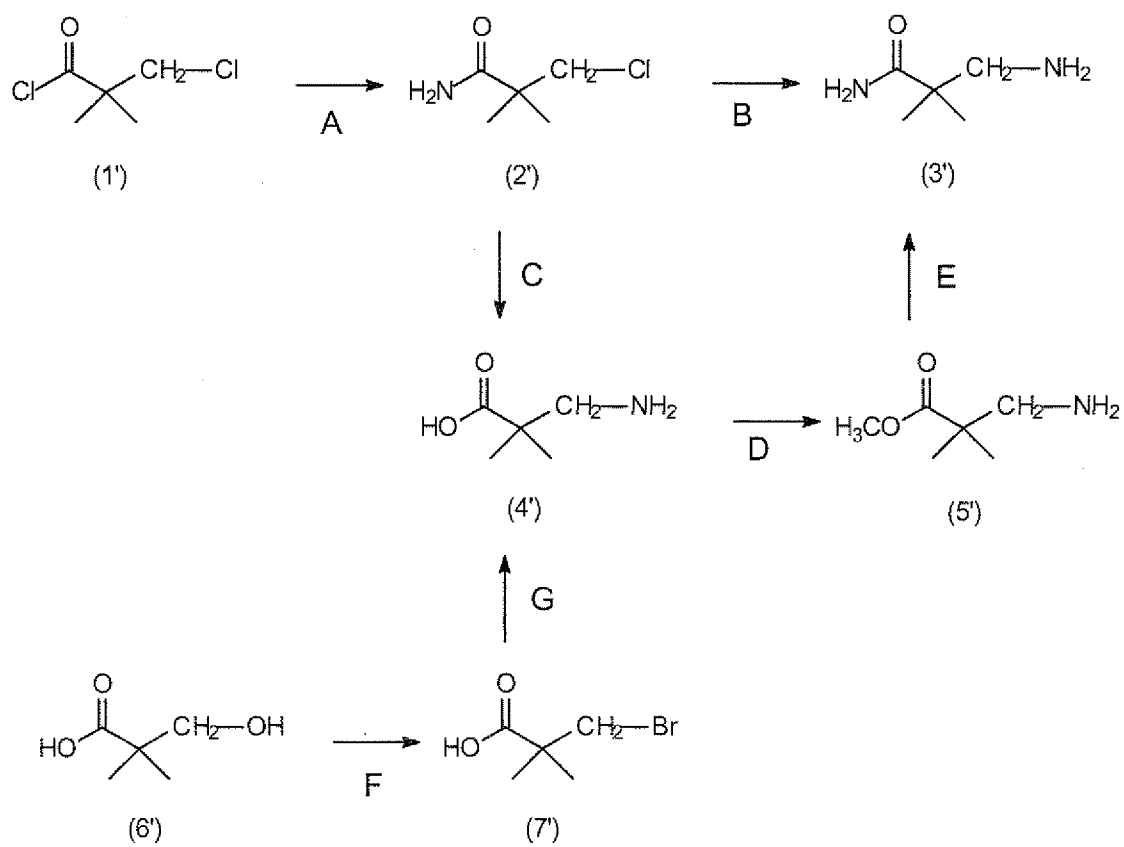


Figure 2