METHOD FOR PREPARING METHIONINE ANALOGUES

The present invention concerns a method for preparing methionine analogues, as well as selenium derivatives of methionine analogues, from abundant and accessible compounds, derived from biomass.

The methionine and the analogues thereof such as 2-hydroxy-4-methylthiobutanoic acid (**HMTBA**) and 2-oxo-4-methylthiobutanoic acid (**KMB**), as well as salts, chelates, in particular metal chelates (of Zn, Ca Mn, Mg, Cu, Na…) and the esters of these acids, such as the isopropyl and tert-butyl esters of HMTBA, are widely used in animal nutrition. The selenium derivatives of the methionine and of the hydroxy-analogues thereof are also constituents of major interests in animal nutrition.

Given the continuously growing volumes, consumed worldwide, of these ingredients, it is necessary to develop manufacturing methods from renewable, energy-efficient and non-polluting sources.

The authors have thus developed a method for preparing these compounds from organic acids, the salts or the derivatives thereof, which may be obtained from biomass, in particular by biological transformations such as fermentation methods.

Summary

In one aspect, the present disclosure refers to a method for preparing a compound or a salt thereof, said compound having the formula (I),

$$\mathbf{R^1OOC\text{-}C(=X)\text{-}CHR^2R^3} \qquad \mathbf{(I)}$$

Where X is selected from O; R^1 represents H or a C1-C6 alkyl group;

R^2 represents H, a C1-C6 alkyl group, or an alkylaryl group; and

R^3 represents CH_2SR^4 or CH_2SeR^4 with R^4 representing H or a C1-C6 alkyl group

from a compound of formula (II), or a salt thereof,

$$\mathbf{R^1OOC\text{-}C(=X)\text{-}CHR^2R^5} \qquad \mathbf{(II)}$$

Where R^1, R^2 and X have the above definition; and

R^5 represents H or $COOR^6$ with R^6 representing H or a C1-C6 alkyl group,

said method being carried out in the presence of a compound of formula (III)

$CH_2(Y)(Z)$ (III)

Where Y represents SR^4 or SeR^4 with R^4 meeting the preceding definition; or NR^8R^9, with R^8 and R^9, identical or different, representing each a C1-C6 alkyl group or an alkylaryl group or together a cyclic hydrocarbon C3-C6 group;

Z, represents OR^{10} with R^{10} representing H, a C1-C6 alkyl group, or $CO-R^4$ with R^4 meeting the preceding definition; or $NR^{11}R^{12}$, with R^{11} and R^{12}, identical or different, representing each, a C1-C6 alkyl group, or an alkylaryl group or together a cyclic hydrocarbon C3-C6 group;

where Z and Y are identical or different, Said method being characterized in that

The compound (II) is reacted with the compound (III) to lead to a non-isolated intermediate having the structure (IV)

$R^1OOC-C(=X)-CHR^2-CH_2Z$ (IV)

Where R^1, R^2, X and Z have the definition above

The compound (IV) thus obtained is reacted with R^4SH or a salt thereof, or R^4SeH or a salt thereof, with R^4 meeting the preceding definition, already present in the reaction medium or added during the method,

Then, upon completion of the reaction, the compound (I) or a salt thereof is isolated.

In another aspect, the present disclosure refers to a compound having the following formula (IV)

$R^1OOC-C(=X)-CHR^2-CH_2Z$ (IV)

Where R^1 represents H or a C1-C6 alkyl group;

X represents O, R2 represents H and Z represents the piperidinyl group.

In a further aspect, the present disclosure refers to a method for manufacturing D, L-methionine, D- or L-methionine, D,L-2-hydroxy-4-methylthiobutanoic acid (HMTBA), D- or L-HMTBA, from 2-oxo-4-methylthiobutanoic acid (KMB), characterized in that it comprises preparing KMB according to a method as disclosed herein, and then KMB is chemically or biologically transformed into methionine or HMTBA.

Detailed Description

According to the invention, this method allows preparing a compound or a salt thereof, said compound having the formula (I),

$$\mathbf{R^1OOC\text{-}C(=X)\text{-}CHR^2R^3} \qquad \mathbf{(I)}$$

Where X is selected from O; N-R' where R' represents H or a C1-C6 alkyl group; and N-OR" where R" represents H, a C1-C6 alkyl group or an alkylaryl group;

R^1 represents H or a C1-C6 alkyl group;

R^2 represents H, a C1-C6 alkyl group, or an alkylaryl group; and

R^3 represents CH_2SR^4 or CH_2SeR^4 with R^4 representing H or a C1-C6 alkyl group,

from a compound of formula (II), or a salt thereof,

$$\mathbf{R^1OOC\text{-}C(=X)\text{-}CH_2R^2R^5} \qquad \mathbf{(II)}$$

Where R^1, R^2 and X have the definition above; and

CLAIMS

1. A method for preparing a compound or a salt thereof, said compound having the formula (I),

$$R^1OOC\text{-}C(=X)\text{-}CHR^2R^3 \qquad (I)$$

Where X is selected from O;

R^1 represents H or a C1-C6 alkyl group;

R^2 represents H, a C1-C6 alkyl group, or an alkylaryl group; and

R^3 represents CH_2SR^4 or CH_2SeR^4 with R^4 representing H or a C1-C6 alkyl group

from a compound of formula (II), or a salt thereof,

$$R^1OOC\text{-}C(=X)\text{-}CHR^2R^5 \qquad (II)$$

Where R^1, R^2 and X have the above definition; and

R^5 represents H or $COOR^6$ with R^6 representing H or a C1-C6 alkyl group,

said method being carried out in the presence of a compound of formula (III)

$$CH_2(Y)(Z) \qquad (III)$$

Where Y represents SR^4 or SeR^4 with R^4 meeting the preceding definition; or NR^8R^9, with R^8 and R^9, identical or different, representing each a C1-C6 alkyl group or an alkylaryl group or together a cyclic hydrocarbon C3-C6 group;

Z represents OR^{10} with R^{10} representing H, a C1-C6 alkyl group, or CO-R^4 with R^4 meeting the preceding definition; or $NR^{11}R^{12}$, with R^{11} and R^{12}, identical or different, representing each, a C1-C6 alkyl group or an alkylaryl group or together a cyclic hydrocarbon C3-C6 group;

where Z and Y are identical or different,

Said method being characterized in that

The compound (II) is reacted with the compound (III) to lead to a non-isolated intermediate having the structure (IV)

$$R^1OOC\text{-}C(=X)\text{-}CHR^2\text{-}CH_2Z \qquad (IV)$$

Where R^1, R^2, X and Z have the definition above

The compound (IV) thus obtained is reacted with R^4SH or a salt thereof, or R^4SeH or a salt thereof, with R^4 meeting the preceding definition, already present in the reaction medium or added during the method,

Then, upon completion of the reaction, the compound (I) or a salt thereof is isolated.

2. The method according to claim 1, characterized in that the compound (II) is reacted with hydrated or non-hydrated formaldehyde or paraformaldehyde, in a basic medium and in the presence of MeSH or a salt thereof.

3. The method according to claim 1, characterized in that the compound of formula (II) is reacted with a compound (III) selected from 1-[(methylsulfanyl)methyl]-piperidine, 1-[(methylsulfanyl)methyl]-pyrrolidine and 1-[(methylsulfanyl)methyl]-diethylamine.

4. The method according to claim 1, characterized in that the compound of formula (II) is reacted with a compound (III) selected from methylenedipiperidine, methylenedipyrrolidine and methylenedi(diethylamine).

5. The method according to any one of the preceding claims, characterized in that the compound (II) is selected from the oxaloacetic acid and the pyruvic acid.

6. The method according to any one of the preceding claims, characterized in that, following the method, 2-oxo-4-methylthiobutanoic acid (KMB) or a salt thereof is obtained, preferably selected from the calcium, sodium, ammonium, manganese, copper, zinc and magnesium salts thereof.

7. A compound having the following formula (IV)

$$R^1OOC\text{-}C(=X)\text{-}CHR^2\text{-}CH_2Z \qquad (IV)$$

Where

R^1 represents H or a C1-C6 alkyl group;

X represents O, R2 represents H and Z represents the piperidinyl group.

8. A method for manufacturing D, L-methionine, D- or L-methionine, D,L-2-hydroxy-4-methylthiobutanoic acid (HMTBA), D- or L-HMTBA, from 2-oxo-4-methylthiobutanoic acid (KMB), characterized in that it comprises preparing KMB according to a method as defined in any one of claims 1 to 6, and then KMB is chemically or biologically transformed into methionine or HMTBA.