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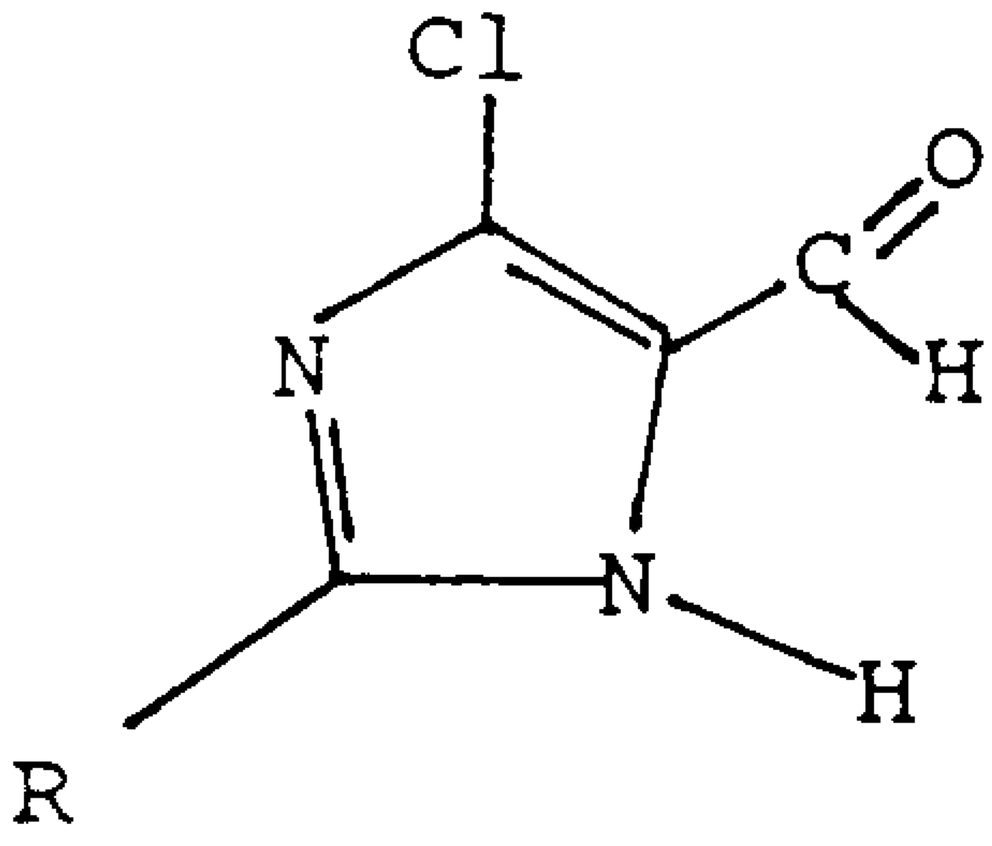
(54) Titre : PROCEDE POUR LA PRODUCTION DE 5-CHLORIMIDAZOLE-4-CARBALDEHYDES SUBSTITUEES EN 2
(54) Title: PROCESS FOR THE PRODUCTION OF 2-SUBSTITUTED-5-CHLORIMIDAZOLE-4-CARBALDEHYDES

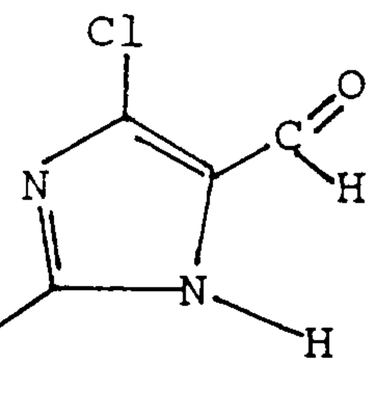


I

(57) Abrégé/Abstract:
A process for the production of 2-substituted-5-chlorimidazole-4-carbaldehydes of the general formula (I): (see formula I) wherein R represents hydrogen, an alkyl group, an alkenyl group, a cycloalkyl group, a benzyl group, or a phenyl group. These compounds are important intermediates for the production of anti-hypertensive pharmaceutical agents and herbicidal compounds.

ABSTRACT

A process for the production of 2-substituted-5-chlorimidazole-4-carbaldehydes of the general formula (I):

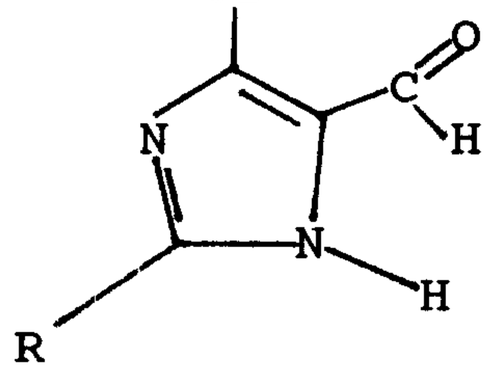


I

wherein

R represents hydrogen, an alkyl group, an alkenyl group, a cycloalkyl group, a benzyl group, or a phenyl group. These compounds are important intermediates for the production of anti-hypertensive pharmaceutical agents and herbicidal compounds.

The present invention relates to a process for the production of a 2-substituted-5-chlorimidazole-4-carbaldehyde of the general formula (I):



I

wherein

R represents hydrogen, an alkyl group, an alkenyl group, a cycloalkyl group, a benzyl group, a phenyl group or an aryl group. The present invention also relates to novel 2-substituted-3,5-dihydroimidazol-4-ones.

Several methods for the production of the 2-substituted-5-chlorimidazole-4-carbaldehydes (I) are known.

United States Patent Number 4,355,040 describes a process according to which 2-amino-3,3-dichloro-acrylonitrile is reacted with an aldehyde to the corresponding azomethine intermediate product and further with a hydrogen halide and water to the corresponding 2-substituted-5-haloimidazole-4-carbaldehyde. Experimental data is lacking in the patent. A great drawback of the synthesis is that the starting material, 2-amino-3,3-dichloroacrylonitrile, has to be produced from dichloro-acetonitrile by reaction with hydrogen cyanide/sodium cyanide. The extremely toxic reactants and the safety measures associated therewith that are required just for the preparation of the starting material, make the entire process unsuitable for industrial-scale production.

In another embodiment, United States Patent Number 4,355,040 discloses a 3-stage process wherein, an amidinehydrochloride is cyclized under high NH_3 pressure

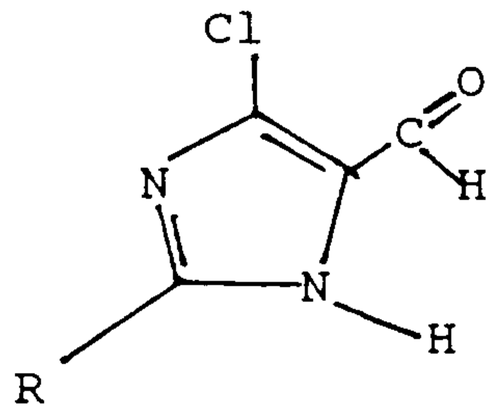
with dihydroxyacetone, the imidazole alcohol is halogenated and finally oxidized to the aldehyde.

It has now been revealed that pressures of over 20 bars are necessary for the cyclization reaction.

The oxidation of the alcohol is achieved according to United States Patent Number 4,355,040 in the presence of chromium oxide. It will be appreciated by those skilled in the art that oxidation with heavy metal oxides, that are not generally recyclable, is no longer justifiable in view of current ecological concerns and requirements.

An object of the present invention is to provide processes that do not have the above-mentioned drawbacks of the prior art.

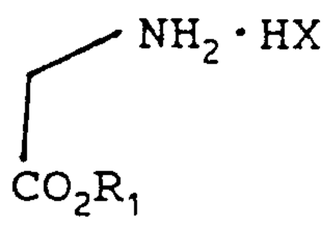
According to one aspect of the present invention, there is provided a process for the production of a 2-substituted-5-chlorimidazole-4-carbaldehyde of the general formula (I):



I

wherein

R represents hydrogen, an alkyl group, an alkenyl group, a cycloalkyl group, a benzyl group, or a phenyl group. The process includes, in a first step, reacting a glycine ester hydrohalide of the general formula (II):

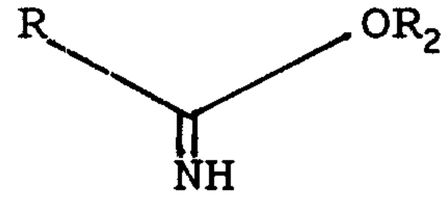


II

wherein

R_1 represents an alkyl group and

X represents a halogen atom, with an imidic acid ester of the general formula (III):

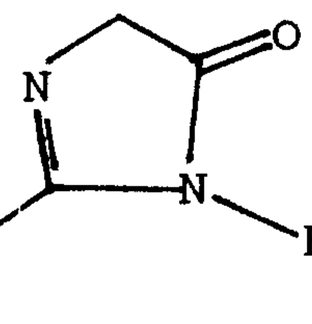


III

wherein

R has the above-mentioned meaning and

R_2 represents an alkyl group, in the presence of a base, to provide a 2-substituted-3,5-dihydroimidazol-4-one of the general formula (IV):



IV

wherein

R has the above-mentioned meaning and, in the second step, reacting the 2-substituted-3,5-dihydroimidazol-4-one (IV) with phosphoroxy chloride in the presence of N,N-dimethylformamide to the end product.

Preferably, an alkali hydroxide or an alkali alcoholate is used as the base in the first stage. Preferably, the reaction in the first stage is performed at a pH in the range of from about 7 to 12. Preferably, the reactants of the first stage, namely, the glycine ester hydrohalide (II), the imidic acid ester (III) and the base, are reacted in the stochiometric molar ratio of 1:1:1. Preferably, the reaction temperature in the first stage is from about -20°C to 50°C. Preferably, the reactants of the second stage, namely, the 2-substituted-3,5-dihydroimidazol-4-one (IV), the phosphoroxy chloride and the N,N-

dimethylformamide, are reacted in a molar ratio of from about 1:1:1 to 1:5:5. Preferably, the reaction temperature in the second stage is from about 50°C to 130°C.

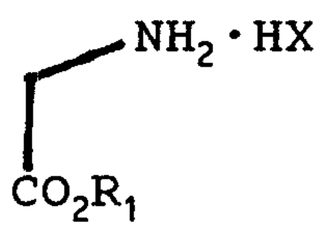
Preferably, the 2-substituted-3,5-dihydro-imidazol-4-one (IV) is not isolated during the process.

According to another aspect of the present invention, there is provided a 2-substituted-3,5-dihydro-imidazol-4-one (IV) wherein

R represents n-propyl, n-butyl, 2-butenyl or 3-butenyl.

The 2-substituted-5-chlorimidazole-4-carbaldehydes (I) are important starting materials for the production of anti-hypertensive pharmaceutical agents (United States Patent Number 4,355,040) and herbicidal compounds (German OS 2804435).

For the production of a 2-substituted-5-chlorimidazole-4-carbaldehyde (I) according to the present invention, in a first step, a glycine ester hydrohalide of the general formula (II):

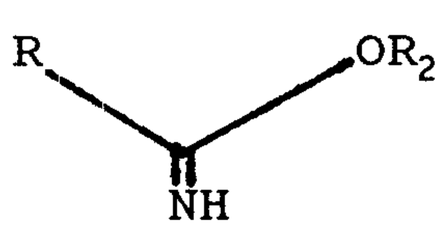


II

wherein

R_1 represents an alkyl group and

X represents a halogen atom, is reacted with an imidic acid ester of the general formula (III):

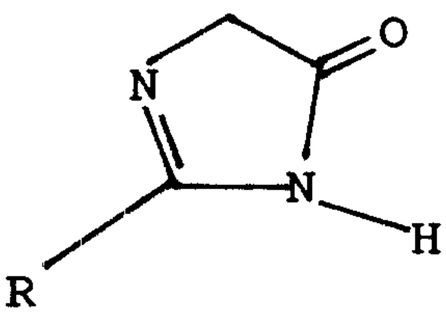


III

wherein

R has the above-mentioned meaning and

R_2 represents an alkyl group, in the presence of a base, to the corresponding 2-substituted-3,5-dihydro-imidazol-4-one of the general formula (IV):



IV

wherein

R has the above-mentioned meaning.

With reference to the substituents, namely R, R_1 and R_2, it will be understood that the designated groups have the following meanings.

An alkyl group is a straight-chain or branched C_1-C_6-alkyl group, such as, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl or hexyl groups. The n-propyl and the n-butyl groups are the preferred alkyl groups for R.

An alkenyl group is a straight-chain or branched C_1-C_6-alkenyl group, such as, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, pentenyl and its isomers, or hexenyl and its isomers. The preferred R_1 alkenyl group substituents are 2-butenyl and 3-butenyl.

Suitable representatives of cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl groups.

Both the benzyl group and the phenyl group can contain substituents, such as, the above-mentioned alkyl groups, halogen atoms, nitro groups or amino groups.

Suitable halogens are chlorine, bromine or iodine. Preferably, the halogen is chlorine.

Suitably, the glycine ester hydrohalide (II) is reacted in the presence of a base, suitably at a pH of from about 7 to 12, preferably from about 9 to 11, with the imidic acid ester (III). The glycine ester hydrohalides (II) are commercially available stable compounds. Suitable

bases are alkali hydroxides, such as, sodium hydroxide or potassium hydroxide, or alkali alcoholates, such as, sodium or potassium methylate, ethylate or tert-butylate. Advantageously, the base is dissolved in a suitable solvent. Especially suitable solvents are aliphatic alcohols, such as, methanol or ethanol. The imidic acid ester (III) is suitably added in the form of a solution in an inert solvent, such as aromatic solvents, including toluene and chlorobenzene, or the above-mentioned aliphatic alcohols.

Advantageously, the reaction of the glycine ester hydrohalide (II), imidic acid ester (III) and base takes place in the stochiometric ratio of 1:1:1. A suitable reaction temperature is in the range of from about -20°C to 50°C, preferably from about 0°C to 25°C.

After a reaction time of a few hours, the corresponding 2-substituted-3,5-dihydroimidazol-4-one (IV) can be isolated by a method known to those skilled in the art, such as by simple filtration, in yields greater than 95 percent.

Advantageously, the resultant reaction mixture is prepared without isolation of the 2-substituted-3,5-dihydroimidazol-4-one (IV) for further processing to the corresponding 2-substituted-5-chlorimidazole-4-carbaldehyde (I) (one-reactor process).

The 2-substituted-3,5-dihydroimidazol-4-ones (IV) resultant in the context of the step, wherein

R represents n-propyl, n-butyl, 2-butenyl or 3-butenyl, are especially preferred. These compounds are not know in the literature and are, therefore, also a component of the present invention.

The first step of the process according to the present invention represents a tremendous improvement over the known process according to R. Jacquier et al., Bull Soc Chim France, 1040;1971, wherein a free glycine ester is reacted with an imidic acid ethyl ester (corresponding to

the general formula III wherein R is limited to methyl, phenyl or benzyl) in the absence of a solvent to the corresponding 3,5-dihydroimidazol-4-one. A disadvantage of the known process is the fact that the free glycine ester is very unstable and, therefore, must be newly synthesized and isolated for every reaction. According to the known process, after a reaction time of 24 hours and more, yields of only 30 to 48% could be obtained.

In the second step, the reaction to the desired 2-substituted-5-chlorimidazole-4-carbaldehyde (I) takes place according to the present invention with phosphoroxy chloride or phosgene in the presence of N,N-dimethyl-formamide. Suitably the molar ratio of the 2-substituted-3,5-dihydroimidazol-4-one (IV) to phosphoroxy chloride or phosgene to N,N-dimethylformamide is in the range of from about 1:1:1 to 1:5:5, preferably at about 1:3:3. The reaction temperature is suitably in the range of from about 50°C to 130°C. Optionally, the second stage reaction can be conducted in the presence of an additional inert solvent.

The isolation of the resultant 2-substituted-5-chlorimidazole-4-carbaldehyde (I) from the reaction mixture takes place advantageously in a manner known to those skilled in the art by extraction with a suitable solvent.

The following Examples illustrate the present invention.

EXAMPLE 1

Production of 2-n-butyl-3,5-dihydroimidazol-4-one

31.71 g (0.25 mol) of glycine methyl ester hydrochloride was added to a solution of 10.1 g (0.25 mol) sodium hydroxide in methanol at 0°C. After 15 minutes, 126.5 g of a 22.8% solution of pentanimidic acid methyl ester in chlorobenzene was added over a period of 5 minutes, dropwise, to the resulting white suspension. The light yellow suspension was stirred for 4 hours at room

temperature and diluted with chlorobenzene (100 ml). The methanol was distilled off at a temperature of 26°C and at a pressure of from 30 to 50 mbar. The resulting orange suspension was diluted with methylene chloride (100 ml) and then filtered. After removal of the solvent from the filtrate, 34.09 g (97%) of 2-n-butyl-3,5-dihydroimidazol-4-one (content >95%, according to GC and ^{1}H-NMR) was obtained.

Data regarding the product was:

^{1}H-NMR ($CDCl_3$, 300 Mhz) δ in ppm	0.95	(t, 3H);
	1.45	(m, 2H);
	1.68	(m, 2H);
	2.48	(t, 2H);
	4.1	(m, 2H);
	9.3	(br. s, 1H).

EXAMPLE 2

Production of 2-n-butyl-5-chlorimidazole-4-carbaldehyde

2-n-Butyl-2-imidazol-5-one (9.81 g, 70 mmol) was added to a solution of phosphoroxychloride (26.83 g, 175 mmol) in chlorobenzene (50 ml) at room temperature. The orange suspension was heated to 100°C within 5 minutes, and then N,N-dimethylformamide (12.79 g, 175 mmol) was added within 3 minutes. The black mixture was kept for 2 hours at 100°C, cooled to 40°C and poured on water (84 ml). After addition of ethyl acetate (42 ml), the mixture was stirred for 15 minutes at 26°C to 28°C and then adjusted to pH 7 by addition of 30% sodium hydroxide solution (67 ml). The phases were separated, and the aqueous phase was extracted twice with aliquots of 70 ml of ethyl acetate. The combined organic phases were dried over $MgSO_4$, filtered and concentrated by evaporation with a rotary evaporator. 2-n-Butyl-5-chlorimidazole-4-carbaldehyde was obtained in

a yield of 8.31 g (64% relative to the 2-n-butyl-2-imidazol-5-one).

EXAMPLE 3

Production of 2-n-butyl-5-chlorimidazole-4-carbaldehyde (Process without isolation of 2-n-butyl-2-imidazol-5-one)

31.71 g (0.25 mol) of glycine methyl ester hydrochloride as a solid was added in one portion to a solution, which had been cooled to 0°C, of 10.17 g (0.25 mol) of sodium hydroxide in methanol (80 ml), and the white suspension (NaCl precipitated out) was cooled to -8°C. The temperature rose to 0°C within 15 minutes, then 127.0 g of a 22.68% solution of pentanimidic acid methyl ester in chlorobenzene (0.25 mol of pentanimidic acid methyl ester) was added over a period of 15 minutes. The temperature was allowed to rise within 1 hour to 21°C, and then the yellowish brown suspension was stirred for 3.5 hours at 21°C. After addition of chlorobenzene (400 ml), approximately 240 g of a mixture of methanol, water and chlorobenzene was distilled off at 30°C. Phosphoroxy chloride (107.33 g, 0.7 mol) was added to the remaining suspension (about 420 g) (temperature rose to 35°C). The cloudy, orange reaction mixture was heated to 100°C, and then N,N-dimethylformamide (51.71 g, 0.70 mol) was added over a period of 5 minutes (the temperature rose to 108°C). After 2 hours at 100°C the black mixture was cooled to 75°C and poured into 300 g of water which had been cooled to 10°C. The mixture was diluted with ethyl acetate (150 ml), stirred for 15 minutes at 50°C and then adjusted to pH 1 by the addition of 160 ml of 30% sodium hydroxide solution. The phases were separated, and the aqueous phase was extracted twice with 250 ml aliquots of ethyl acetate. The combined organic phases were dried over $MgSO_4$, filtered and concentrated by evaporation with a rotary evaporator. 2-n-Butyl-5-chlorimidazole-4-carbaldehyde was obtained in a

yield of 34.3 g (73% relative to the glycine methyl ester hydrochloride).

EXAMPLE 4

Production of 2-n-butyl-5-chlorimidazole-4-carbaldehyde

(Process without isolation of 2-n-butyl-2-imidazol-5-one)

31.72 g (0.25 mol) of glycine methyl ester hydrochloride as a solid was added in one portion to a solution, which had been cooled to 0°C, of 10.15 g (0.25 mol) of sodium hydroxide in methanol (80 ml) and the white suspension (NaCl precipitated out) was cooled to -9°C. The temperature rose to 0°C within 15 minutes, and then 127.0 g of a 22.68% solution of pentanimidic acid methyl ester in chlorobenzene (0.25 mol of pentanimidic acid methyl ester) was added over a period of 15 minutes. The temperature was allowed to rise within 1 hour to 21°C, and then the yellowish brown suspension was stirred for 3.5 hours at 21°C. After addition of chlorobenzene (200 ml), approximately 210 g of a mixture of methanol, water and chlorobenzene was distilled off at 30°C. Phosphoroxy chloride (107.33 g, 0.70 mol) was added to the remaining suspension (about 226 g) (temperature rose to 35°C). The cloudy, orange reaction mixture was heated to 100°C, and then N,N-dimethylformamide (51.71 g, 0.70 mol) was added over a period of 5 minutes (the temperature rose to 108°C). After 2 hours at 100°C, the black mixture was cooled to 40°C and poured in 300 g of water which had been cooled to 10°C. The mixture was diluted with ethyl acetate (150 ml), heated for 15 minutes at 50°C and adjusted to pH 1 by addition of 160 ml of 30% sodium hydroxide solution. The phases were separated, and the aqueous phase was extracted twice with 250 ml aliquots of ethyl acetate. The combined organic phases were dried over $MgSO_4$, filtered and concentrated by evaporation with a rotary evaporator to 125 g and cooled to -10°C. The precipitated product was

filtered off, washed with cold ethyl acetate and dried at 50°C. The yield was 19.01 g (40% relative to the glycine methyl ester hydrochloride). The mother liquor contained, according to GC with internal standard, another 11.66 g of 2-n-butyl-5-chlorimidazole-4-carbaldehyde was obtained. Thus, the total yield was 65% relative to the glycine methyl ester hydrochloride.

EXAMPLE 5

Production of 2-n-propyl-3,5-dihydroimidazol-4-one

17.39 g (138 mmol) of glycine methyl ester hydrochloride was added to a solution of sodium hydroxide (5.56 g, 139 mmol) in methanol (55 ml) at 0°C. After 15 minutes, 14.50 g (content 96.3%, 138 mmol) of butanimidic acid methyl ester was added to the white suspension over a period of 8 minutes. The mixture was stirred for 3 hours at room temperature and then concentrated by evaporation with a rotary evaporator. The residue was mixed with CH_2Cl_2 (250 ml) and the resultant suspension was filtered. The filtrate was concentrated by evaporation with a rotary evaporator, again mixed with CH_2Cl_2 (250 ml) and filtered again. After removal of the solvent, 2-n-propyl-3,5-dihydroimidazol-4-one was obtained (15.13 g, content >95% according to ^{1}H-NMR, 83% yield). Other data concerning the product were:

^{1}H-NMR ($CDCl_3$, 400 Mhz) δ in ppm 1.03 (t, 3H);
1.75 (m, 2H);
2.46 (t, 2H);
4.12 (s, 2H);
9.98 (br. s, 1H).

EXAMPLE 6

Production of 2-n-propyl-5-chlorimidazole-4-carbaldehyde

N,N-dimethylformamide (7.04 g, 96.3 mmol) was added to a mixture of 2-n-propyl-3,5-dihydroimidazol-4-one (4.49 g, 35.6 mmol) and $POCl_3$ (14.76 g, 96.3 mmol) in chlorobenzene (40 ml) at 100°C. The mixture was heated for 2 hours at 100°C, cooled and poured over 40 g of ice. The mixture was adjusted to pH 1 by the addition of 30% sodium hydroxide solution (22.5 ml) and the phases were separated. The aqueous phase was extracted twice with 40 ml aliquots of ethyl acetate and the combined organic phases were washed with water (20 ml) and filtered with silica gel. After removal of the solvent from the filtrate, 2.79 g of a light brown solid was obtained. Recrystallization from ethyl acetate/petroleum ether yielded 2-n-propyl-5-chlorimidazole-4-carbaldehyde (2.04 g, 33%). The product had a melting point of from 133.3°C to 137.5°C. Other data concerning the product were:

^{1}H-NMR ($CDCl_3$, 400 Mhz) δ in ppm 1.01 (t, 3H);
1.84 (m, 2H);
2.83 (t, 2H);
9.64 (s, 1H);
11.56 (br. s, 1H).

EXAMPLE 7

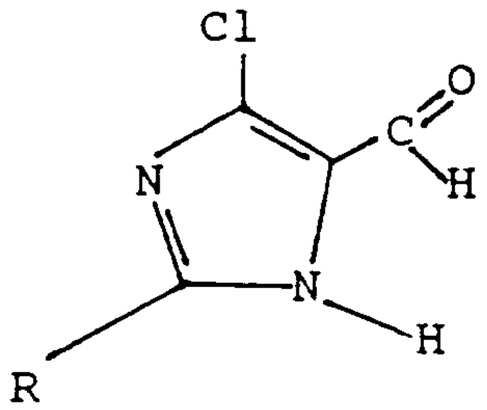
Production of 2-but-2-enyl-3,5-dihydroimidazol-4-one

2-But-2-enyl-3,5-dihydroimidazol-4-one was produced by reaction of glycine methyl ester hydrochloride and 3-pentenimidic acid methyl ester by the method described in Example 1. Data concerning the product were:

^{1}H-NMR ($CDCl_3$, 400 Mhz) δ in ppm 1.75 (d, 3H);
3.19 (d, 2H);
4.12 (s, 2H);
5.54 (m, 1H);
5.75 (m, 1H);
9.20 (br. s, 1H).

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

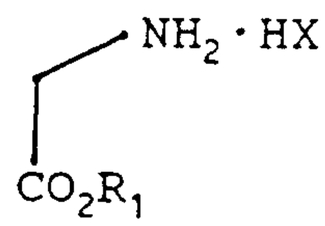
1. A process for the production of a 2-substituted-5-chlorimidazole-4-carbaldehyde of the general formula (I):



I

wherein

R represents hydrogen, an alkyl group, an alkenyl group, a cycloalkyl group, a benzyl group, or a phenyl group, comprising, in a first step reacting a glycine ester hydrohalide of the general formula (II):

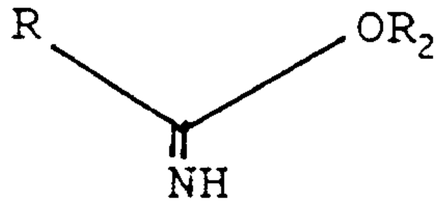


II

wherein

R_1 represents an alkyl group and

X represents a halogen atom, with an imidic acid ester of the general formula (III):

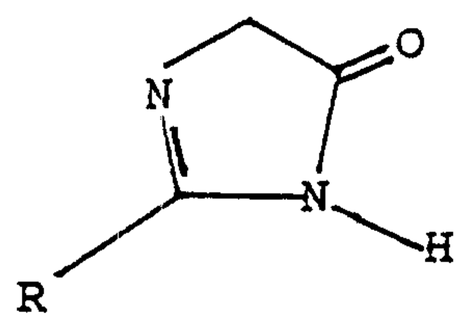


III

wherein

R has the above-mentioned meaning and

R_2 represents an alkyl group, in the presence of a base, to produce a 2-substituted-3,5-dihydroimidazol-4-one of the general formula (IV):



IV

wherein

R has the above-mentioned meaning and, in a second step, reacting the 2-substituted-3,5-dihydro-imidazol-4-one (IV) with phosphoroxy chloride or phosgene in the presence of N,N-dimethylformamide.

2. A process according to claim 1, wherein the base is an alkali hydroxide or an alkali alcoholate.

3. A process according to claim 1 or 2, wherein the reaction in the first step is performed at a pH in the range of from about 7 to 12.

4. A process according to claim 1 or 2, wherein the glycine ester hydrohalide (II), the imidic acid ester (III) and the base are reacted in a stochiometric molar ratio of about 1:1:1.

5. A process according to claim 1 or 2, wherein the reaction in the first stage is conducted at a temperature of from about -20°C to 50°C.

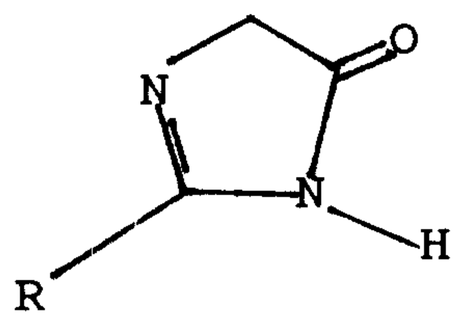
6. A process according to claim 1 or 2, wherein the 2-substituted-3,5-dihydroimidazol-4-one (IV), phosphoroxy chloride or phosgene and N,N-dimethylformamide are reacted in a molar ratio of from about 1:1:1 to 1:5:5.

7. A process according to claim 1 or 2, wherein the 2-substituted-3,5-dihydroimidazol-4-one (IV), phosphoroxy chloride or phosgene and N,N-dimethylformamide are reacted in a molar ratio of about 1:3:3.

8. A process according to claim 1 or 2, wherein the reaction in the second stage is conducted at a temperature of from about 50°C to 130°C.

9. A process according to claim 1 or 2, wherein the 2-substituted-3,5-dihydroimidazol-4-one (IV) is not isolated during the process.

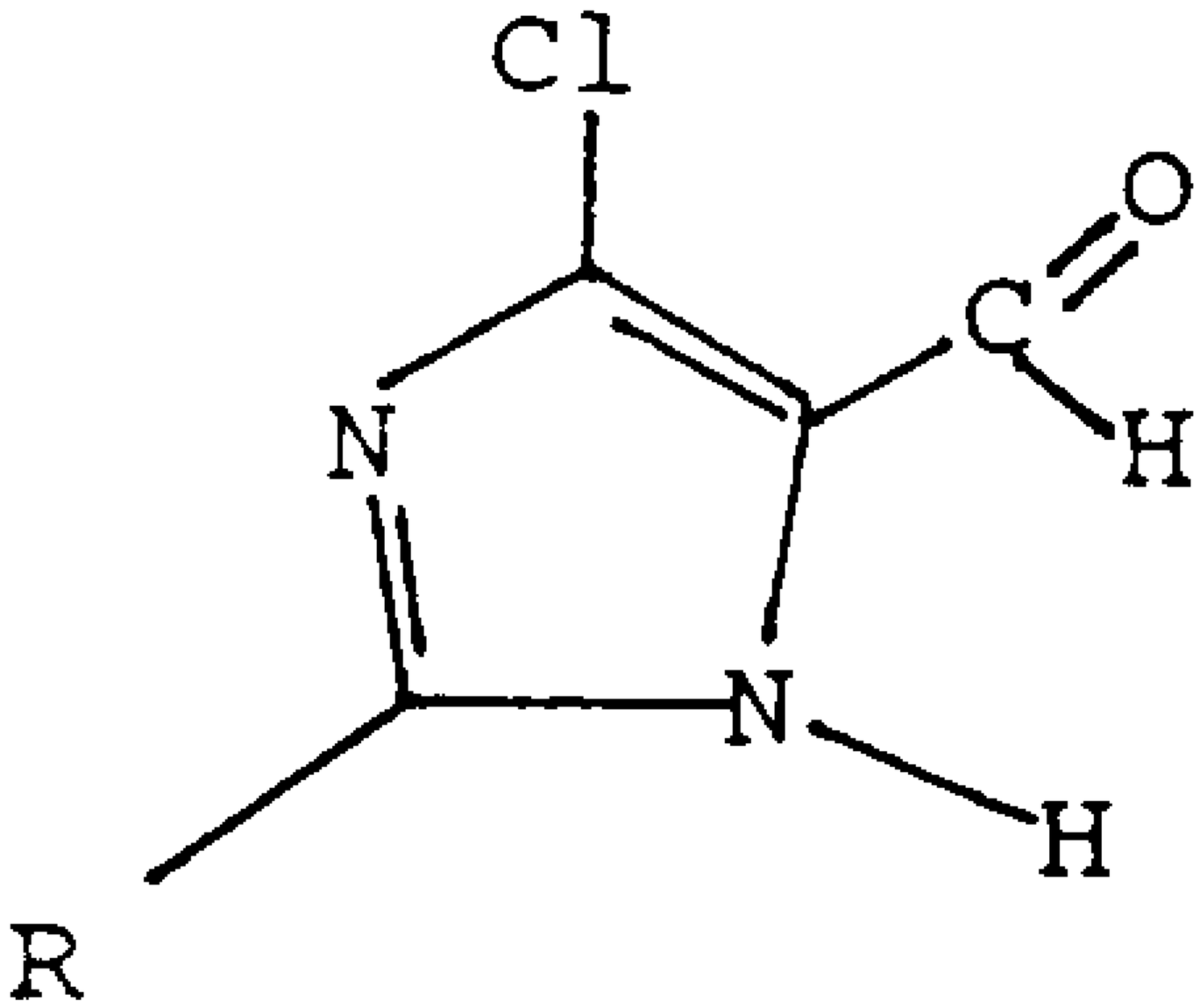
10. A 2-substituted-3,5-dihydroimidazol-4-one of the general formula (IV):



IV

wherein

R represents n-propyl, n-butyl, 2-butenyl or 3-butenyl.



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