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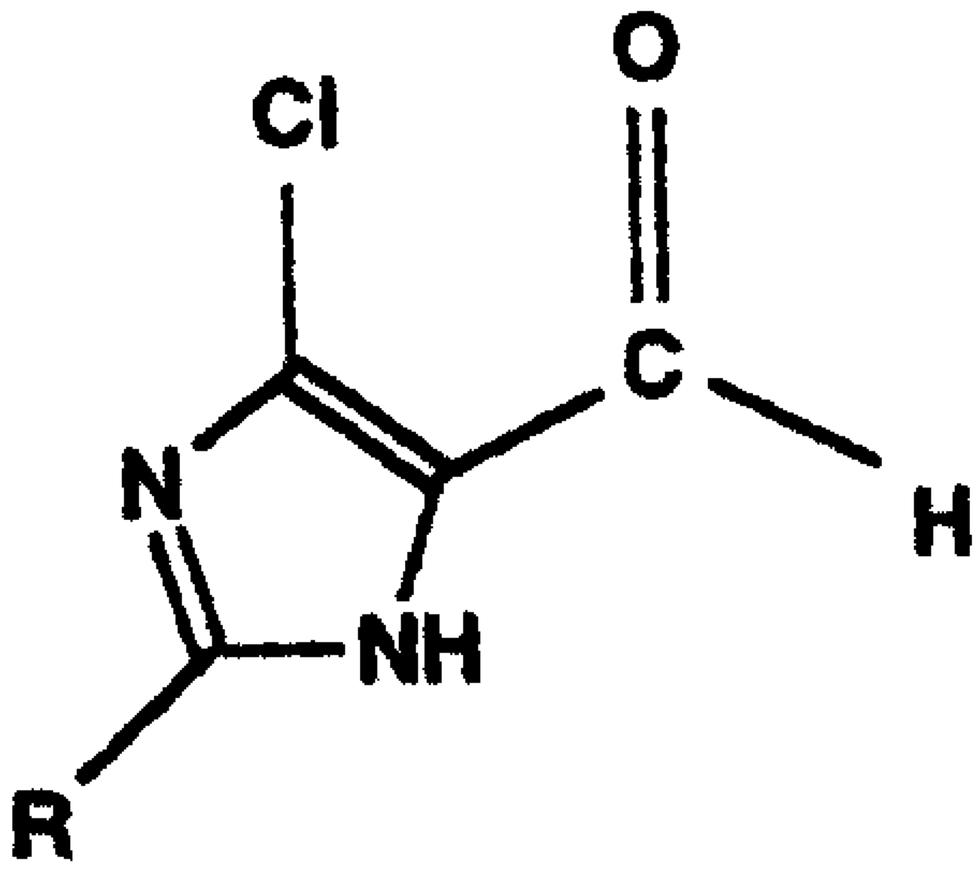
(54) Titre : PROCEDE D'OBTENTION DE 5-CHLORIMIDAZOLE-4-CARBALDEHYDES A SUBSTITUANT EN 2
(54) Title: PROCESS FOR THE PRODUCTION OF 2-SUBSTITUTED-5-CHLORIMIDAZOLE-4-CARBALDEHYDES



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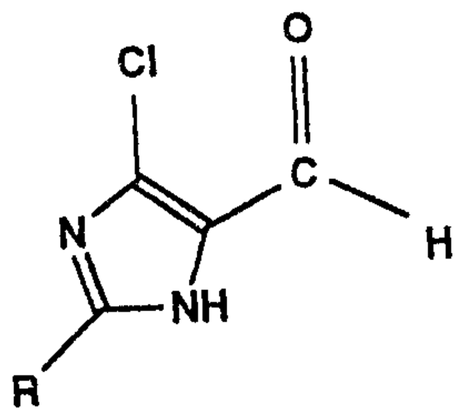
(57) Abrégé/Abstract:
A process for the production of a 2-substituted-5-chlorimidazole-4-carbaldehyde of the general formula: (see formula I) wherein R represents an alkyl, cycloalkyl, benzyl, phenyl or aryl group. The compound is a valuable intermediate for the production of antihypertensive pharmaceutical agents and herbicidal compounds. Preferably, a novel compound 2-n-butyl-3,5-dihydroimidazolin-4-one is used to produce 2-n-butyl-5-chlorimidazole-4-carbaldehyde (I, Wherein R represents n-butyl).

ABSTRACT OF THE DISCLOSURE

A process for the production of a 2-substituted-5-chlorimidazole-4-carbaldehyde of the general formula:



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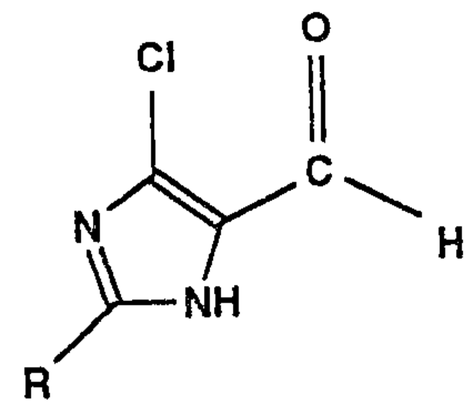
wherein R represents an alkyl, cycloalkyl, benzyl, phenyl or aryl group. The compound is a valuable intermediate for the production of antihypertensive pharmaceutical agents and herbicidal compounds. Preferably, a novel compound 2-n-butyl-3,5-dihydroimidazolin-4-one is used to produce 2-n-butyl-5-chlorimidazole-4-carbaldehyde (I, wherein R represents n-butyl).

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



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wherein R represents an alkyl, cycloalkyl, benzyl, phenyl or aryl group. The alkyl group can be a straight chain or a branched C_1-C_6 alkyl group, such as, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl and hexyl groups. n-Butyl is a preferred alkyl group. Cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl groups are suitable representatives of the cycloalkyl group. The benzyl and phenyl groups can contain substituents, such as, the aforementioned alkyl groups plus halogen atoms, nitro groups and amino groups.

2-Substituted-5-chlorimidazole-4-carbaldehydes (I) are important starting materials for the production of antihypertensive pharmaceutical agents (United States Patent Number 4,355,040) and herbicidal compounds (German Published Patent Application Number 2,804,435).

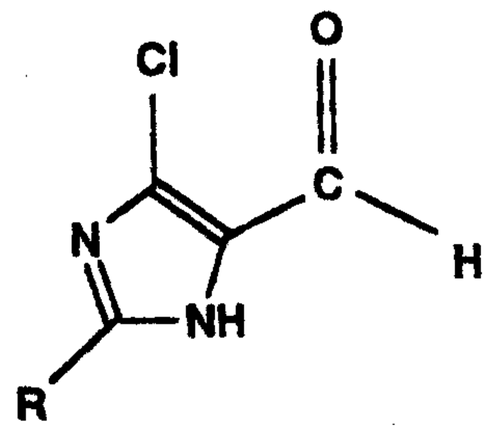
Several methods for the production of 2-substituted-5-chlorimidazole-4-carbaldehydes (I) are known.

United States Patent Number 4,355,040 describes a process wherein 2-amino-3,3-dichloro-acrylonitrile is reacted with an aldehyde to form the corresponding intermediate azomethine. The intermediate is reacted with a hydrogen halide and water to produce 2-substituted-5-haloimidazole-4-carbaldehyde. A drawback of the synthesis is that 2-amino-3,3-dichloroacrylonitrile is produced from dichloroacetonitrile by reaction with hydrogen cyanide/sodium cyanide. The reactant is extremely toxic and the required safety measures render the process unsuitable for industrial-scale production.

US 4,355,040 also discloses an alternate three-stage process, wherein, in a first stage, an amidinehydrochloride is subjected to a ring closure reaction under high NH_3 pressure with dihydroxyacetone. The resultant imidazole alcohol is then halogenated and finally oxidized to the corresponding aldehyde. One drawback is that pressures of greater than 20 bars are necessary for the ring closure reaction. Another drawback is that the alcohol is oxidized in the presence of chromium oxide. Heavy metal oxides including chromium oxide, are not generally recyclable. Accordingly, the process is not viable from an environmental standpoint.

An object of the present invention is to provide a process that overcomes the above-mentioned drawbacks.

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:



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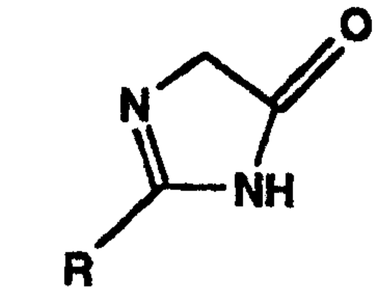
wherein R represents an alkyl, cycloalkyl, benzyl, phenyl, or aryl group, comprising the step of reacting a 2-substituted-3,5-dihydroimidazolin-4-one of the general formula:

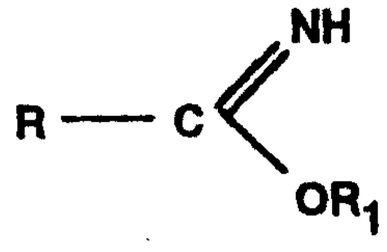


II

wherein R has the above-stated meaning, with phosphorus oxychloride in the presence of N,N-dimethylformamide.

According to another aspect of the present invention, there is provided 2-n-butyl-3,5-dihydro-imidazolin-4-one.

2-Substituted-3,5-dihydroimidazolin-4-one of the general formula II can be produced, in a manner known to those skilled in the art, (for example, R. Jacquier et al, Bull. Soc. Chim. France, 1040 f; 1971) by the reaction of a substituted imidic acid alkyl ester of the general formula:



III

wherein R has the above-stated meaning and R_1 represents a lower alkyl group having 1 to 4 C atoms with a glycine lower alkyl ester. Preferably, glycine ethyl ester is reacted with pentanimidic acid ethyl ester (III, wherein R represents n-butyl and R_1 represents ethyl) to synthesize 2-n-butyl-3,5-dihydroimidazolin-4-one (II, wherein R represents n-butyl). This compound is not known in the literature and therefore also constitutes an aspect of the invention.

2-Substituted-3,5-dihydromidazolin-4-one (II) is reacted with phosphorus oxychloride and N,N-dimethylformamide to produce 2-substituted-5-chlorimidazole-4-carbaldehyde (I). Suitably, phosphorus oxychloride and N,N-dimethylformamide are first introduced to the reaction vessel in a molar ratio of from about 2:1 to about 4:1. The corresponding 2-substituted-3,5-dihydroimidazolin-4-one (II) is then suitably added to the reaction mixture. The reaction advantageously takes place at a temperature in the range of from about 50 to 80°C.

The end product can be purified in a manner known to those skilled in the art.

Preferably 2-n-butyl-3,5-dihydroimidazolin-4-one is used to produce 2-n-butyl-5-chlorimidazole-4-carbaldehyde in the process of the present invention.

The following Examples illustrate the invention.

Example 1

Preparation of 2-n-butyl-3,5-dihydroimidazolin-4-one

A mixture of glycine ethyl ester (24.5 g, 221 mmol) and pentanimidic acid ethyl ester (34.5 g, 254 mmol) was stored at -18°C for 36 hours. The precipitate was filtered, washed with ice-cold diethyl ether (70 ml) and dried. The yield of the product was 10.51 g (34%). The product had a melting point in the range of from 79.5 to 80.5°C. Further product data include:

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

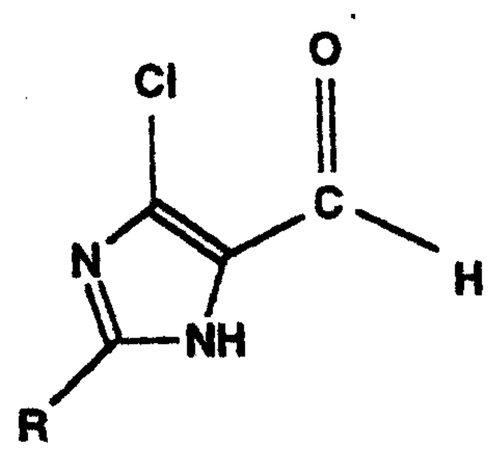
Example 2

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

N,N-dimethylformamide (3.65 g, 50 mmol) was instilled in $POCl_3$ (30.65 g, 200 mmol) at approximately 20°C. The reddish mixture was stirred for 15 minutes at 20°C. 2-n-Butyl-3,5-dihydroimidazolin-4-one (1.40 g, 10 mmol) was then added in portions and the mixture was heated for 1 hour at 80°C. Excess $POCl_3$ was removed on a rotary evaporator and the oily residue was poured over ice. The pH was adjusted to 7 with a saturated $NaHCO_3$ solution and the mixture was extracted three times each with 150 ml of ethyl acetate. The combined organic phases were dried ($MgSO_4$), filtered and evaporated. Purification of the crude product by column chromatography with silica gel yielded 2-n-butyl-5-chlorimidazole-4-carbaldehyde. The yield of the product was 0.25 g, 14%, content about 95% (^{1}H-NMR).

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:



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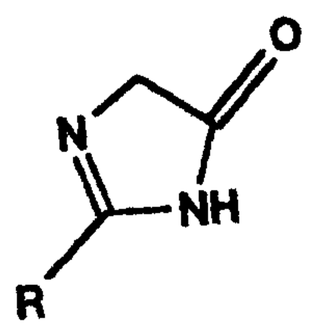
wherein R represents an alkyl, cycloalkyl, benzyl, or aryl group, wherein a 2-substituted-3,5-dihydroimidazolin-4-one of the general formula:



II

wherein R has the above-stated meaning, is reacted with phosphorus oxychloride in the presence of N,N-dimethylformamide.

2. A process according to Claim 1, wherein R represents a phenyl group.

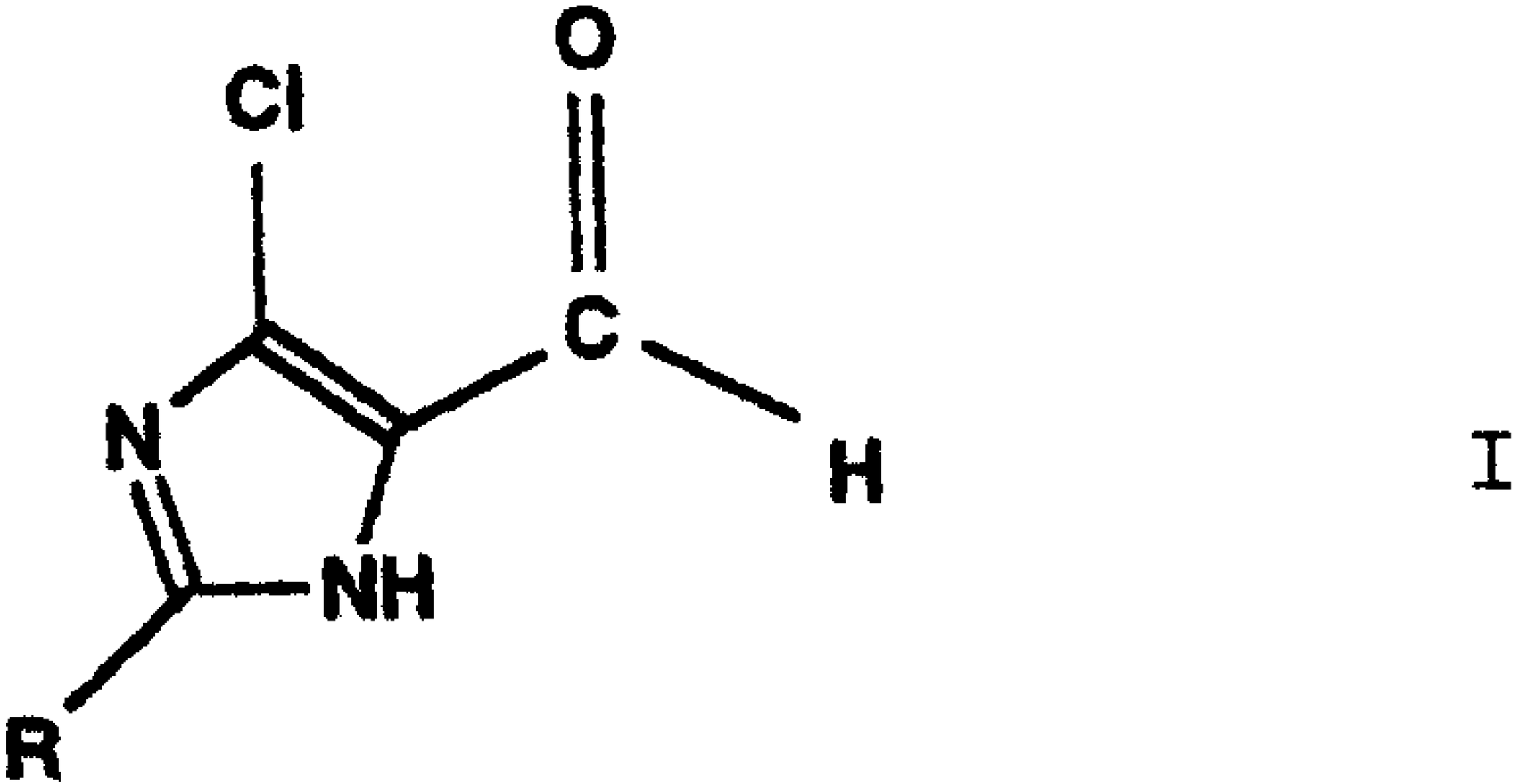
3. A process according to Claim 1, wherein the 2-substituted-3,5-dihydroimidazolin-4-one is 2-n-butyl-3,5-dihydroimidazolin-4-one.

4. A process according to Claim 1 or 2, wherein the reaction of phosphorus oxychloride and N,N-dimethylformamide takes place in a molar ratio of phosphorus oxychloride to N,N-dimethylformamide of from about 2:1 to about 4:1.

5. A process according to Claim 1 or 2, wherein the reaction takes place at a temperature in the range of from about 50 to 80°C.

6. A process according to Claim 3, wherein the reaction takes place at a temperature in the range of from about 50 to 80°C.

7. 2-n-Butyl-3,5-dihydroimidazolin-4-one.



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