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(54) Titre : METHODE DE PREPARATION DE CARBOXAMIDES DE COMPOSES HETEROCYCLIQUES AROMATIQUES RENFERMANT DE L'AZOTE; UTILISATION DE CES PRODUITS

(54) Title: PROCESS FOR THE PREPARATION OF CARBOXAMIDES OF NITROGEN-CONTAINING AROMATIC HETEROCYCLIC COMPOUNDS AND THEIR USE

(57) Abrégé/Abstract:
A process for the preparation of a carboxamide of a nitrogen-containing aromatic heterocyclic compound is described. The novel process is a carbamoylation process wherein the corresponding nitrogen-containing aromatic heterocyclic compound is reacted with formamide in the presence of peroxodisulphuric acid or a peroxodisulphate. The use of a carboxamide of a nitrogen-containing aromatic heterocyclic compound for the preparation of the corresponding carboxylic acid by alkaline hydrolysis is also described.

ABSTRACT OF THE DISCLOSURE

A process for the preparation of a carboxamide of a nitrogen-containing aromatic heterocyclic compound is described. The novel process is a carbamoylation process wherein the corresponding nitrogen-containing aromatic heterocyclic compound is reacted with formamide in the presence of peroxodisulphuric acid or a peroxodisulphate. The use of a carboxamide of a nitrogen-containing aromatic heterocyclic compound for the preparation of the corresponding carboxylic acid by alkaline hydrolysis is also described.

The present invention relates to a novel process for the preparation of carboxamides of nitrogen-containing aromatic heterocyclic compounds (N-heterocyclic compounds) and to the use of carboxamides thus obtained for the preparation of the corresponding carboxylic acids by alkaline hydrolysis.

Carboxamides and carboxylic acids of N-heterocyclic compounds are important intermediate products for the preparation of pharmaceuticals.

A carbamoylation method for N-heterocyclic compounds is known from German Patent Number 2,056,433. This process is distinguished by the fact that a redox system of

R-OOH + iron(II)

wherein R represents hydrogen, an alkyl or a cycloalkyl group, is used for formation of the carbamoyl radical. However, iron(II) must be used in stochiometric amounts or even in excess. It will be appreciated by those skilled in the art that the use of iron(II) results in significant waste water and waste product problems in the case of industrial scale synthesis. Furthermore, the alkyl hydroperoxides are expensive and hazardous to handle because of their explosiveness.

It is an object of the present invention to develop a carbamoylation process which can be employed on an industrial scale and can overcome the disadvantages of the prior art processes.

According to an aspect of the present invention, there is provided a process for the preparation of a carboxamide of a nitrogen-containing aromatic heterocyclic compound, comprising the step of reacting a nitrogen-containing aromatic heterocyclic compound with formamide in the presence of peroxodisulphuric acid or a peroxodisulphate.

According to another aspect of the present invention, there is provided the use of a carboxamide of a nitrogen-containing aromatic heterocyclic compound for the

preparation of the corresponding carboxylic acid by alkaline hydrolysis.

N-heterocyclic compounds are understood to represent compounds selected from the group comprising pyridines, quinolines, isoquinolines, pyrimidines, pyridazines, pyrazines, quinoxalines, quinazolines, acridines and benzimidazoles. These compounds can optionally have one or more substituents selected from the group comprising alkyl, alkoxy, alkanoyl, alkoxycarbonyl, arylalkyl, aryloxycarbonyl, halogen, carboxyl, cyano, amino, alkylamino and dialkylamino groups. Suitable alkyl groups are linear or branched and expediently have from 1 to 6, preferably from 1 to 4 carbon atoms. A suitable aryl group is a phenyl group which is optionally substituted by one or more of the substituents mentioned hereinbefore. Suitable halogens are fluorine, chlorine, bromine or iodine.

Formamide is expediently added in an amount of from about 3 to 35 mol, preferably in an amount of from about 5 to 6 mol, per mol of the N-heterocyclic compound. Peroxodisulphuric acid or peroxodisulphate is advantageously metered into the mixture in a slight excess, namely in an amount of from about 1.1 to 3.0 mol per mol of the N-heterocyclic compound. The peroxodisulphates of peroxodisulphuric acid are preferred. Suitable peroxodisulphates are peroxodisulphates of sodium, potassium or ammonium.

To improve the selectivity of the carbamoylation, the reaction is advantageously carried out in the presence of a strong acid, preferably in the presence of sulphuric acid.

The addition of a solvent is not essential, since in principle an excess amount of formamide can also function as a solvent. Nevertheless, it is possible to carry out the reaction in the presence of a polar inert solvent. Acetonitrile is particularly suitable.

The reaction temperature is from about 20 to 80°C, preferably from about 65 to 75°C.

The resulting carboxamide can be isolated from the reaction mixture, in a manner known to those skilled in the art, after a relatively short period of time after the addition of peroxodisulphuric acid or peroxodisulphate. As a rule, the carboxamide is obtained in a good yield of greater than 80% and in a high purity.

Depending on the substituents of the N-heterocyclic compounds, two carboxamide functions can be introduced according to the present invention. This is the case in particular with "electron-donating" groups, such as, for example, alkyl groups. The reaction according to the invention of 4-methylpyridine thus results in 4-methylpyridine-2,6-dicarboxamide.

The resulting carboxamides can either be isolated or hydrolysed directly under alkaline conditions to produce the corresponding carboxylic acids. If the carboxamides prepared according to the present invention contain CN groups as substituents, these are as a rule likewise hydrolysed to carboxylic acid. Alkaline hydrolysis of the 4-cyano-2-pyridine-carboxamide prepared from 4-cyano-pyridine thus results in pyridine-2,4-dicarboxylic acid, which is an important intermediate product for pharmaceuticals.

The following Examples illustrate the invention.

Example 1

a) Preparation of 4-cyano-2-pyridine-carboxamide

85 g (0.82 mol) of 4-cyanopyridine were initially introduced into 700 ml of acetonitrile at room temperature and 32.4 g (0.32 mol) of 98% strength sulphuric acid were added. The resulting white suspension was heated to 60°C, after which 201.3 g (4.47 mol) of formamide in 52 g of water were added. The resulting clear solution was heated to 70°C, after which 281.3 g (1.23 mol) of ammonium

peroxodisulphate were metered into the solution in portions over a period of 2 hours (exothermic). After all of the ammonium peroxodisulphate was added, stirring was continued at 74°C for 75 minutes. 880 ml of water were then added and the water/acetonitrile azeotrope was distilled off in vacuo. The white-yellow suspension was then filtered at 80°C and the filter cake was washed with water heated to 80°C and dried in vacuo. 117 g (87.4%) of 4-cyano-2-pyridine-carboxamide were obtained with a content of about 90% (HPLC).

b) Preparation of pyridine-2,4-dicarboxylic acid

80 g (0.5 mol) of 4-cyano-2-pyridine-carboxamide were suspended in 155 ml of water. 170.3 g of 30% strength sodium hydroxide solution were then added dropwise at 80°C over a period of 30 minutes, after which a yellow solution was formed. After the solution had been stirred for 30 minutes, it was brought to pH 1.5 with concentrated hydrochloric acid. The resulting white suspension was cooled and filtered and the filter cake was washed with water. Thereafter, the filter cake was suspended again in water, the pH was brought to 1 with hydrochloric acid and the solid was dissolved at 95°C. When subsequently allowed to cool, the pyridine-2,4-dicarboxylic acid crystallized as the monohydrate. After drying in vacuo at 115°C, 75 g (83.1%) of anhydrous 4-cyano-2-pyridine-carboxamide were obtained with a content of greater than 97% (HPLC).

The following Examples 1 through 9 were carried out analogously to Example 1a:

Example	Starting Material	Product	Yield
2	Pyridine-2,3-dicarboxylic acid	5-Carbamoyl-pyridine-2,3-dicarboxylic acid	70%
3	4-Methylpyridine	4-Methylpyridine-2,6-dicarboxamide	81%
4	4-Chloropyridine	4-Chloropyridine-2-carboxamide	55%
5	2-Methyl-5-ethyl-pyridine	6-Methyl-3-ethyl-pyridine-2-carboxamide	40%
6	2,5-Dimethyl-pyrazine	3,6-Dimethyl-2,5-pyrazine-dicarboxamide	15%
7	2-Methylquinoline	2-Methyl-4-quinoline-carboxamide	90%
8	6-Methyl-2-pyridine-carbonitrile	6-Cyano-2-methyl-3-pyridine-carboxamide	25%
9	6-Chloro-2-pyridine-carbonitrile	6-Cyano-2-chloro-3-pyridine-carboxamide	30%

Example 10

Preparation of pyridine-2,4-dicarboxylic acid from isonicotinic acid

80 g (0.65 mol) of isonicotinic acid were suspended in 600 ml of acetonitrile at room temperature. 26 g (0.26 mol) of 98% strength sulphuric acid, 161 g (3.58 mol) of formamide and 42.4 g of water were then added. The suspension was heated to 70°C, after which 208.7 g (0.91) mol of ammonium peroxodisulphate were added in portions such that the temperature did not exceed 75°C. After the mixture had been stirred at 73°C for 90 minutes, 650 ml of water were added. Thereafter, the suspension was filtered

and the filter cake was washed with 150 ml of water. The resulting 2-carbamoylpyridine-4-carboxylic acid was then suspended in 350 ml of water and the suspension was heated to 80°C. 208 g of 30% strength sodium hydroxide solution (1.56 mol) were then added over a period of 15 minutes. The mixture was then subsequently stirred until no further evolution of NH_3 was observed. The residual NH_3 was removed by heating the solution to 95°C.

After careful acidification of the solution to pH 1 with concentrated HCl and subsequent cooling, pyridine-2,4-dicarboxylic acid crystallized out. The suspension was filtered at 5°C. The resulting product was then dissolved in 800 ml of boiling water, acidified to pH 1 with concentrated HCl and recrystallized by subsequent cooling. After filtration, the material was washed on a filter with water and dried in vacuo. 81.5 g (75%) of pyridine-2,4-dicarboxylic acid were obtained with a content, according to HPLC, of greater than 98%.

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

1. A process for the preparation of a carboxamide of a nitrogen-containing aromatic heterocyclic compound, comprising the step of reacting a nitrogen-containing aromatic heterocyclic compound selected from the group consisting of pyridines and quinolines with formamide in the presence of peroxodisulphuric acid or a peroxodisulphate and a strong acid.

2. A process according to claim 1, wherein the reaction is carried out in the presence of a peroxodisulphate.

3. A process according to claim 2, wherein the peroxodisulphate is ammonium peroxodisulphate.

4. A process according to claim 1, 2 or 3, wherein the concentration of peroxodisulphuric acid or peroxodisulphate is from about 1.1 to 3.0 mol per mol of the nitrogen-containing aromatic heterocyclic compound.

5. A process according to claim 1, 2 or 3, wherein the concentration of formamide is in the range of from about 3 to 35 mol per mol of the nitrogen-containing aromatic heterocyclic compound.

6. A process according to any one of claims 1 to 5, wherein the strong acid is sulfuric acid.

7. A process according to claim 1, 2 or 3, wherein the reaction is conducted at a temperature in the range of from about 20 to 80°C.