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(54) PROCESS FOR THE PRODUCTION OF 4-ACYLAMIDO-4,4-DICARBALKOXY BUTANAL PHENYL HYDRAZONE

(71) We, DEUTSCHE GOLD-UND SILBER-SCHEIDEANSTALT VORMALS ROESSLER a body corporate organised under the laws of Germany of 9 Weissfrauenstrasse, 6 Frankfurt Main 1, Germany do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:

This invention relates to a process for the production of 4-acylamido-4,4-dicarbalkoxy butanal phenyl hydrazone.

More particularly the invention relates to a process for the production of 4-acylamido-4,4-dicarbalkoxy butanal phenyl hydrazone by chemical addition of an acylamido malonic ester to acrolein in the presence of a catalyst and subsequently reacting, in a weakly acid solution, the 4-acylamido-4,4-dicarbalkoxy butanal formed with phenyl hydrazine.

There are already numerous processes for producing 4-acylamido-4,4-dicarbalkoxy butanal phenyl hydrazone - an important intermediate product in the synthesis of tryptophane by Warner and Moe's method - which essentially differ from one another in the conditions applied for the Michael addition of the acylamido malonic ester with the acrolein:

J. Am. Chem. Soc. *70* (1949), pages 2763 *et seq*, describes the Michael addition in the presence of sodium alcoholates. In the most favourable case (using benzene as solvent and sodium methylate as catalyst), the yield of phenyl hydrazone amounts to 87%.

Bull. Agr. Chem. Soc. Japan *21* (1957), pages 58 *et seq*, describes the Michael addition in the presence of sodium methylate, sodium hydrozide, potassium hydroxide, potassium carbonate, sodium cyanide, barium hydroxide, diethyl and triethyl amine or basic ion exchanger resins. The yields of phenyl hydrazone amount to between 60 and 77%.

German Auslegeschrift No. 2,134,360 describes the Michael addition in aqueous suspension in the presence of sodium hydroxide. The yield of phenyl hydrazone is said to be quantitative, although a highly impure product is formed.

The present invention provides a process for the production of 4-acylamido-4,4-dicarbalkoxy butanal phenyl hydrazone which comprises chemical addition of an acylamido-malonic ester to acrolein in the presence of at least one alkali metal salt of a carboxylic acid as catalyst and subsequent reaction of the 4-acylamido-4,4-dicarbalkoxy butanal formed with phenyl hydrazine.

In contrast to the strongly basic catalysts used in the known processes, the alkali metal salts of carboxylic acids are not typical catalysts for the Michael addition. Although they are unable to catalyse the addition of acylamidomalonic esters with acrylonitrile or with esters of acrylic acid, their presence surprisingly promotes a high conversion level in the addition with acrolein. Another important advantage of the catalysts used in the process according to the invention is their lower basicity by comparison with typical known catalysts for the Michael addition. As a result, undesirable secondary reactions involving the acrolein are largely avoided and the 4-acylamido-4,4-dicarbalkoxy butanal or its phenyl hydrazone are obtained in highly pure form.

Catalysts particularly suitable for the process according to the invention are the alkali metal salts of carboxylic acids containing from 2 to 7 carbon atoms, for example, the lithium, sodium and/or potassium salts of saturated fatty acids, such as acetic acid, propionic acid, butyric acid, valeric acid, caproic acid or caprylic acid, or of benzoic acid. Sodium and/or potassium acetate are particularly preferred. The catalysts may be used either individually or in admixture. In order to obtain an adequate reaction velocity, it is best to use the catalysts in a quantity of at least 3g per mole of acylamidomalonic ester used. Any increase in the amount of catalyst to beyond 20g per mole of acylamidomalonic ester used affords no apparent advantages and, accordingly, would appear to be uneconomical.

The preferred acylamidomalonic ester is acetamidomalonic acid diethyl ester. The addition reaction with the acrolein is with advantage carried out in alcohols or in mixtures of alcohols and water as solvent, methanol or ethanol and mixtures thereof with water being particularly suitable. Where the catalyst used is substantially insoluble in the solvent used, it is best added in the form of a solution in water. The Michael addition may even be carried out in aqueous suspension, although in this case the reaction time is longer.

The exothermic addition reaction is best carried out at a temperature of from +5°C to 40°C and preferably at a temperature of from 10°C to 25°C.

The 4-acylamido-4,4-dicarbalkoxy butanal formed during the Michael addition is reacted with phenyl hydrazine in known manner in a weakly acid solution for example acetic acid. The phenyl hydrazone formed may be isolated, for example by filtration. However, it may also be cyclised without intermediate isolation using aqueous sulphuric acid to form skatylacylamidomalonic ester (the next stage in the synthesis of trytophane by Warner and Moe's method).

The invention is illustrated by the following Examples:

Example 1

0.5 mole (108.6g) of acetamidomalonic acid diethyl ester, 10g of sodium acetate ($NaAc.3H_2O$) and 190ml of methanol are introduced into a stirrer-equipped flask provided with an inlet pipe, thermomoter and reflux condenser. 0.525 mole (29.4g) of acrolein are stirred in over a period of 45 minutes, during which the temperature is kept at 15 to 25°C by occasional cooling. The clear colourless solution is after-reacted for 75 minutes at around 20°C. Following the addition of 25ml of glacial acetic acid and 0.525 mole (56.8g) of phenyl hydrazine, the temperature rises to around 35°C. After 10 to 20 minutes, the mixture is heated under reflux for 1 hour to boiling point. After cooling to 15°C, the reaction mixture is filtered under suction and washed, first with a little cold methanol and then with water and dried. The yield of colourless, pure 4-acetamido-4,4-dicarbethoxy butanal phenyl hydrazone amounts to 176.5g, corresponding to 97.2% of the theoretical. Melting point: 138-139°C.

Example 2

0.5 mole (108.6g) of acetamidomalonic acid diethyl ester, 8g of potassium acetate and 200ml of 70% aqueous methyl alcohol are introduced into a stirrer-equipped flask provided with an inlet pipe, thermometer and reflux condenser. 0.525 mole (29.4g) of acrolein are stirred in in three portions over a period of 30 minutes. The reaction temperature is kept between 10 and 25°C. 75 minutes' after-reaction is allowed at 20°C. The reaction with phenyl hydrazine and isolation are carried out in the same way as in Example 1. The yield amounts to 174.9g of colourless product, corresponding to 96.3% of the theoretical. Melting point:137°C.

Example 3

0.25 mole (54.3g) of acetamidomalonic acid diethyl ester, 5g of sodium acetate (dissolved in 5ml of water) and 100ml of ethyl alcohol are introduced into a stirrer-equipped vessel. 0.255 mole (14.3g) of acrolein are stirred in over a period of 1 hour, during which the temperature is kept at 15 to 25°C. 75 minutes' after-reaction is allowed at approximately 20°C. 12ml of glacial acetic acid and 0.25 mole (27.0g) of phenyl hydrazine are poured into the colourless solution, followed after 20 minutes by heating for 1 hour to 75°C. The phenyl hydrazone formed is further processed without isolation and cyclised by heating with aqueous sulphuric acid. Initially ethyl alcohol is distilled off, after which the mixture is boiled under reflux.

The yield of light brown skatylacetamido malonic ester amounts to 76.8g, corresponding to 88.7% of the theoretical. Melting point: 151-153°C.

Example 4

0.5 mole (108.6g) of acetamidomalonic acid diethyl ester, 2g of sodium n-butyrate and 200ml of methanol are introduced into a stirrer-equipped flask provided with an inlet pipe, thermomoter and reflux condenser. 0.525 mole (29.4g) of acrolein are stirred in over a period of 45 minutes. The temperature is kept between 20 and 25°C. 2 hours' after-reaction at 25°C.

The reaction with phenyl hydrazine and

isolation are carried out in the same way as in Example 1.

The yield of colourless phenyl hydrazone amounts to 176g, corresponding to 96.9% of the theoretical. Melting point: 138-139°C.

Example 5

0.5 mole (108.6g) of acetamidomalonic acid diethyl ester, 7.5g of lithium benzoate and 200ml of methanol are introduced into a stirrer-equipped flask provided with an inlet pipe, thermometer and reflux condenser. 0.525 mole (29.4g) of acrolein are stirred in in three portions over a period of 45 minutes, during which the temperature is kept at 15 to 25°C. 1 hour's after-reaction is allowed at 20°C. The reaction with phenyl hydrazine and isolation are carried out in the same way as in Example 1.

The yield of colourless phenyl hydrazone amounts to 173.2g, corresponding to 95.4% of the theoretical. Melting point: 137-138°C.

WHAT WE CLAIM IS:

1. A process for the production of 4-acylamido-4,4-dicarbalkoxy butanal phenyl hydrazone which comprises chemical addition of an acylamidomalonic ester to acrolein in the presence of at least one alkali metal salt of a carboxylic acid as catalyst and subsequent reaction, in a weakly acid solution, of the 4-acylamido-4,4-dicarbalkoxy butanal formed with phenyl hydrazine.

2. A process as claimed in Claim 1, wherein at least one alkali metal salt of a carboxylic acid containing from 2 to 7 carbon atoms is used as catalyst.

3. A process as claimed in Claim 2, wherein sodium and/or potassium acetate is used as catalyst.

4. A process as claimed in any of Claims 1 to 3, wherein the catalyst is used in a quantity of from 3 to 20g per mole of acylamidomalonic ester used.

5. A process for the production of 4-acylamido-4,4-dicarbalkoxy butanal phenyl hydrazone substantially as described with particular reference to any of the Examples.

6. 4-Acylamido-4,4-dicarbalkoxy butanal phenyl hydrazone when produced by a process as claimed in any of Claims 1 to 5.

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