

The present invention relates to a chemically original process for the preparation of known unsymmetrical 1,4-dihydropyridinedicarboxylic esters.

Several processes for their preparation have already been disclosed.

Thus, for example, DE-AS (German Published Specification) 2,117,573 describes the one-step preparation of unsymmetrical dihydropyridines by reaction of aldehydes with keto carboxylic acids and enamino carboxylic esters. A two-step process is regarded as having disadvantages, since the ylidene-keto carboxylic esters, which can be prepared from aldehydes and keto carboxylic esters, are very difficult to isolate in the pure form and then frequently only in low yields.

However, it emerges that one-step preparation of dihydropyridines gives rise to impurities which can be removed only with difficulty by purification processes.

Having regard to the use of unsymmetrical 1,4-dihydropyridines as medicaments, there is a continuous need to make these compounds available in a high degree of purity. Thus, for example, on preparation of 4-(2'-nitrophenyl)-2,6-dimethyl-3,5-dicarboethoxy-1,4-dihydropyridine by the method of US Patent 3,485,847, seven by-products could be detected by thin-layer chromatography.

In the earlier German Applications DE-A 2,841,667, DE-A 2,210,672, DE-A 2,549,568 and DE-A-2,335,466, processes for the preparation of unsymmetrical dihydropyridine esters have already been described. Processes for the preparation of dihydropyridines, which are known as Knoevenagel condensation, are also described in Organic Reaction, Vol. 15 (1967) pages 204-206, 265, 271 and 478. The use of basis catalysts has also been proposed in connection with the known COPE process.

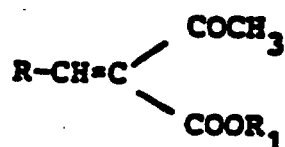
The invention relates to a process for the preparation of unsymmetrical 1,4-dihydropyridines of the general formula I

in which

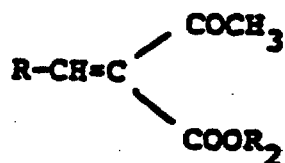
R represents a phenyl radical which is optionally mono- or disubstituted by nitro and/or chlorine and

R₁ represents a C₁-C₄-alkyl radical which is optionally substituted by a C₁-C₄-alkoxy group, and

R₂ represents a C₁-C₁₂-alkyl radical which is optionally substituted by a C₁-C₄-alkoxy group, a trifluoromethyl group or the radical [C₆H₅CH₂] [CH₃]N, the radicals R₁ and R₂ not being identical, by reaction of an ylidene compound of the formulae II or III.

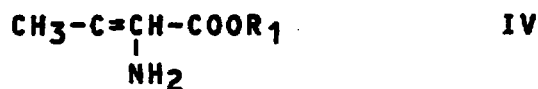


II



III

with an enamine compound of the formulae IV or V



characterized in that the ylidene compound of the formulae II or III is prepared by reaction of a keto carboxylic ester of the formulae VI or VII



with an aldehyde of the formula $RCHO$, in an organic solvent alcohol, in the presence of catalytic amounts of piperidine acetate, at temperatures from $-10^{\circ}C$ to $100^{\circ}C$.

The solvents which are preferably used are aliphatic alcohols, such as methanol, ethanol and/or isopropanol. The preferred reaction temperatures are $20-60^{\circ}C$.

The catalyst is preferably added in amounts from 0.01 to 0.7 mole, particularly preferably from 0.02 to 0.2 mole, especially from 0.04 to 0.2 mole, per mole of keto carboxylic ester.

It is possible and preferred to use 1 to 2 mole, especially 1 mole, of aldehyde per mole of keto carboxylic acid of the formula IV.

In the formula I,
R preferably denotes a 2- or 3-nitrophenyl radical, a 2- or 3-chlorophenyl radical or a 2,3-dichlorophenyl radical,
R₁ preferably denotes methyl, ethyl, propyl, isopropyl, isobutyl or a propoxyethyl radical, and
R₂ preferably denotes methyl, ethyl, propyl, isopropyl, isobutyl, n-decyl, methoxyethyl, propoxyethyl, trifluoromethylmethyl, or the radical $[C_6H_5CH_2]$ $[CH_3]N$.

The reaction of the ylidene compound of the formulae II or III with the enamine compound of the formulae IV or V is carried out at temperatures from -10 to $130^{\circ}C$, preferably from 50 to $100^{\circ}C$.

It is possible and preferred to employ 1 to 1.5 mole, particularly preferably 1 to 1.3, especially 1 to 1.2 mole, of the enamine compound per mole of ylidene compound.

According to a particular embodiment, the crystalline ylidene compound remains in the reaction vessel and is directly reacted with the enamine compound.

It has to be denoted extremely surprising that, in the reaction according to the invention in the presence of the catalysts mentioned, the ylidene-3-keto

carboxylic esters are produced in high purity and excellent yield and can be very readily isolated.

Furthermore, it has to be denoted surprising that the 1,4-dihydropyridine compounds are produced in such high purity and can be isolated in the manner described. Omitting a further purification process, they contain no by-products.

The process according to the invention has a number of advantages.

Thus, the yield is higher than according to the known processes, and the isolated product need not undergo any further purification steps.

The invention may be illustrated by means of the examples which follow:

Example 1

a) Ylidene carboxylic ester

In the following sequence, 80 g (0.5 mole) of 2-methoxyethyl acetoacetate, 75.5 g (0.5 mole) of 3-nitrobenzaldehyde, 1.8 g (0.03 mole) of glacial acetic acid and 2.5 g (0.03 mole) of piperidine are added, with stirring at room temperature, to 325 ml of isopropanol.

The mixture is warmed to 40°C and kept at this temperature for 30 minutes.

It is then cooled to 20°C and stirred for 16 hours. Thereafter it is cooled to 0°C and stirred at this temperature for 1 hour. The supernatant solution is then removed by aspiration, and the crystals are washed with 166 ml of ice-cold isopropanol.

The resulting 2-methoxyethyl 2-(3-nitrobenzylidene)acetoacetate is immediately reacted in the same vessel, as described in b).

If the 2-methoxyethyl 2-(3-nitrobenzylidene)acetoacetate is isolated and dried, then 132 g of pale brown crystals are obtained (90% of the theoretical yield) of melting point 68 - 72°C.

b) 270 ml of isopropanol and 64.4 g (0.45 mole) of isopropyl 3-aminocrotonate are added to the 2-methoxyethyl 2-(3-nitrobenzylidene)acetoacetate which has been prepared according to a) and is moist with isopropanol.

The mixture is heated to reflux (83°C) and kept at this temperature for 24 hours.

After cooling to 0°C, the resulting crystals are isolated, washed with 86 ml of isopropanol and sucked dry.

173.2 g of isopropyl 2-methoxyethyl 4-(3-nitrophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate of melting point 122-127°C (92% of theory) are obtained.

10 Thin-layer chromatography on Merck silica gel precoated plates (mobile phase: chloroform : acetone : petroleum ether = 3 : 2 : 5) shows no visible by-products.

Example 2

15 In analogy to Example 1 there is obtained from the ethyl 3-introbenzylidene-acetoacetate prepared according to Example 1a) and methyl 3-aminocrotonate, after heating in ethanolic solution for 10 hours and subsequent standing at 20°C for 16 hours, 3-methyl 5-ethyl 2,6-dimethyl-4-(3'-introphenyl)-1,4-dihydropyridine-3,5-dicarboxylate, 20 which is recrystallized from methanol (melting point 159°C; yield 83% of theory).

Example 3

a) Ylidene carboxylic ester

25 In the following sequence, 58 g (0.5 mole) of methyl acetoacetate, 82.5 g (1.5 mole) of 2,3-dichlorobenzaldehyde, 18 g (0.03 mole) of glacial acetic acid and 2.5 g (0.03 mole) of piperidine are added, with stirring at room temperature, to 325 ml of isopropanol.

30 The mixture is warmed to 40°C and kept at this temperature for 30 minutes.

It is then cooled to 20°C and stirred for 16 hours. Thereafter it is cooled to 0°C and stirred at this temperature for 1 hour.

35 The resulting 2-(2,3-dichlorobenzylidene)acetoacetate is immediately reacted in the same vessel, as described in b).

b) 270 ml of isopropanol and 58.9 g (0.45 mole) of ethyl 3-aminocrotonate are added to the methyl 2-(2,3-dichlorobenzylidene)acetoacetate which has been prepared according

to a). The mixture is heated to reflux (83°C) and kept at this temperature for 24 hours.

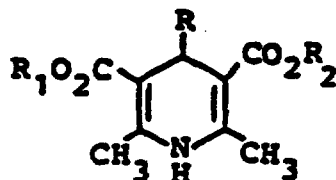
After cooling to 0°C, the resulting crystals are isolated, washed with 86 ml of isopropanol and sucked
5 dry.

138 g of methyl ethyl 4-(2,3-dichlorophenyl)-2,6-methyl-1,4-dihydropyridine-3,5 -dicarboxylate melting point 146°C (80% of theory) are obtained.



Patent Claims

1. Process for the preparation of unsymmetrical 1,4-dihydropyridines of the formula I



I

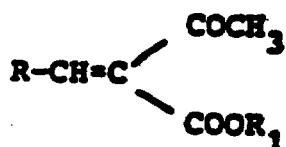
in which

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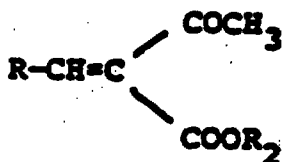
R₁ represents a C₁-C₄-alkyl radical which is optionally substituted by a C₁-C₄-alkoxy group, and

R₂ represents a C₁-C₁₂-alkyl radical which is optionally substituted by a C₁-C₄-alkoxy group, a trifluoromethyl group or the radical [C₆H₅CH₂] [CH₃]N, the radicals R₁ and R₂ not being identical,

by reaction of an ylidene compound of the formulae II or

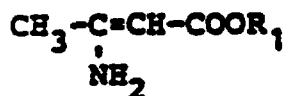


II

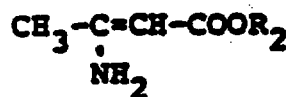


III

with an enamine compound of the formulae IV or V



IV



V

characterised in that the ylidene compound of the formulae II or III is prepared by reaction of a keto carboxylic ester of the formulae VI or VII



with an aldehyde of the formula RCHO , in an organic solvent (lower aliphatic alcohol), in the presence of catalytic amounts of piperidine acetate, at temperatures from -10°C to 100°C .

2. Process according to Claim 1, characterised in that the reaction for preparing the ylidene compound is carried out at $20-60^\circ\text{C}$.
3. Process according to Claim 1, characterised in that 0.01 to 0.7 mole of piperidine acetate is employed per mole of the keto carboxylic ester.
4. Process according to Claim 1, characterised in that 1 to 2 mole of aldehyde is employed per mole of keto carboxylic acid.

