

NEW MANUFACTURING PROCESS

Field of the invention

5 The present invention relates to an improved method for the manufacture of felodipine (ethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridine-dicarboxylate) via the route of reacting 2,3-dichlorobenzylideneacetylacetic acid-methylester (in the following dichlorobenzylidene for short) with ethyl 3-aminocrotonate.

10 Prior art

EP 7293 discloses a method for the preparation of felodipine using dichlorobenzylidene and ethyl 3-aminocrotonate as starting materials. The solvent used is tertiary butanol. No catalyst is used. The reaction time is long, that is 90 minutes or more.

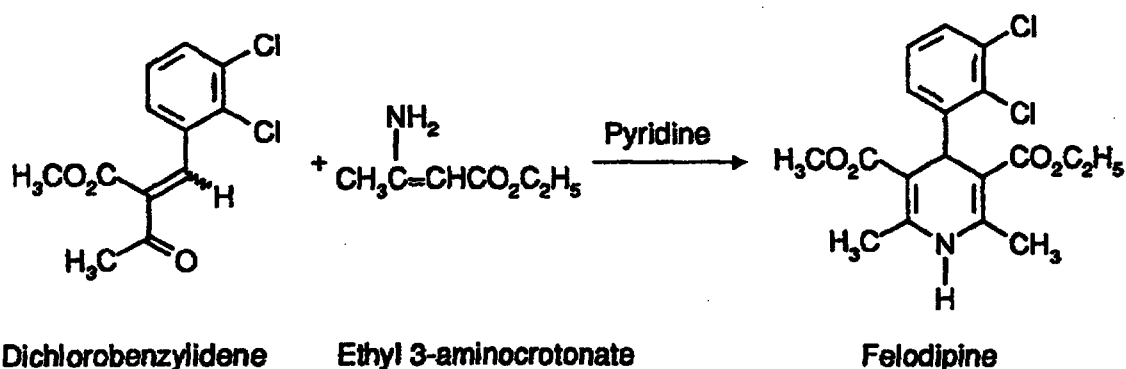
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US 5 310 917 discloses a method for the preparation of felodipine using dichlorobenzylidene and ethyl 3-aminocrotonate as starting materials. The solvent used is ethanol.

20 Disclosure of the invention

It has now been found that felodipine, which is a calcium-channel blocker, can be prepared in a manner that is fast, environmentally sound and gives a good yield using starting materials that are known per se. The new method uses pyridine as a catalyst in combination
25 with an alcohol as solvent.

The method is described by the reaction scheme below:



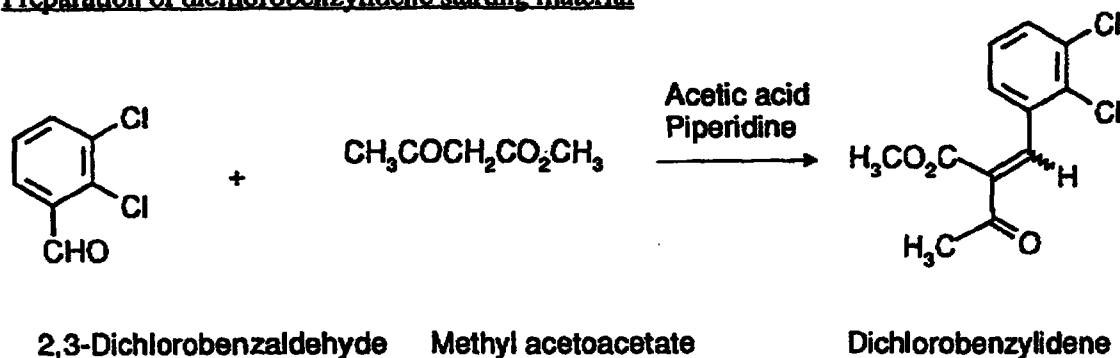
Dichlorobenzylidene is reacted with ethyl 3-aminocrotonate in the presence of pyridine in refluxing alcohol, such as methanol, ethanol or propanol, preferably ethanol. Preferably, the alcohol is then evaporated at reduced pressure and ethyl acetate or methylene chloride is added. The solution can be purified by acidic and neutral aqueous extractions. The solvent can be removed by evaporation. The product can be dissolved in acetone or diisopropyl ether, crystallized by cooling, isolated by filtration and finally washed with acetone, or diisopropyl ether.

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Dichlorobenzylidene is reacted with ethyl 3-aminocrotonate (0.5-0.9 g/g dichlorobenzylidene, preferably 0.58-0.60 g/g dichlorobenzylidene). The reactants are charged together with the solvent alcohol (preferably ethanol 2.5-4.8 ml/g, preferably 3.2-3.9 ml ethanol/g dichlorobenzylidene) and the catalyst pyridine (0.03-0.2 ml/g dichlorobenzylidene, preferably 0.035-0.045 g/g dichlorobenzylidene).

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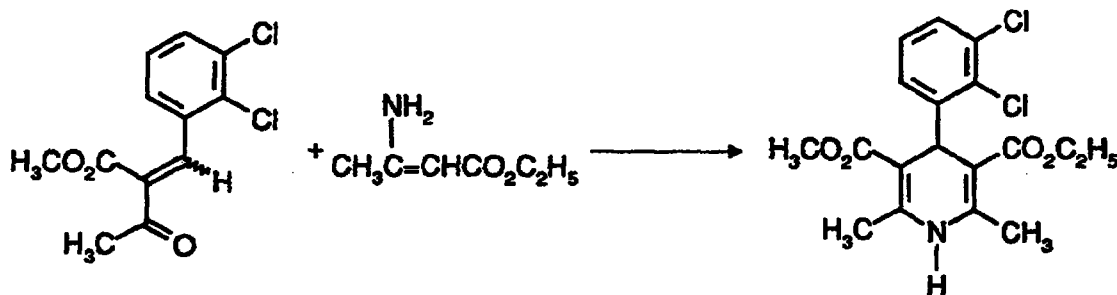
Preparation of dichlorobenzylidene starting material



2,3-Dichlorobenzaldehyde is reacted with methyl acetoacetate in a suitable solvent in the presence of a catalytic amount of acetic acid and piperidine. Water is azeotropically separated off during the reaction. The reaction mixture is extracted in order to remove the catalysts. The solvent is evaporated and methanol is added. The product is crystallized by cooling the solution, isolated by filtration and finally washed with methanol.

Working examples

Example 1



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Dichlorobenzylidene

Ethyl 3-aminocrotonate

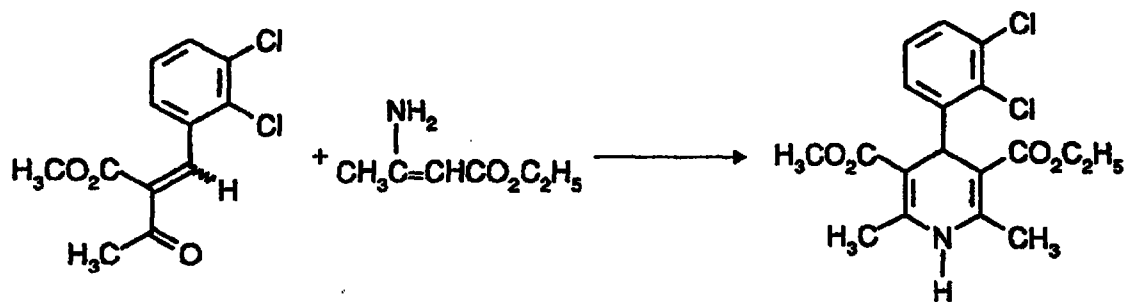
Felodipine

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35.3 g of dichlorobenzylidene was reacted with 20.7 g of ethyl 3-aminocrotonate in the presence of 1.3 g of pyridine in refluxing ethanol (91 ml). Ethanol was evaporated under reduced pressure and ethyl acetate (195 ml) was added in order to dissolve the residue. The solution was purified by acidic extraction (7.3 g of (HCl (aqueous) in 30 ml of H₂O). The solvent was evaporated and acetone (116 ml) was added. The product was crystallized by cooling the solution to -10°C, isolated by filtration and washed with acetone.

Yield: Approximately 85%

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Example 2

5 Dichlorobenzylidene

Ethyl 3-aminocrotonate

Felodipine

30.3 g of dichlorobenzylidene was reacted with 17.8 g of ethyl 3-aminocrotonate in the presence of 5.9 g of pyridine in refluxing ethanol (94 ml). Ethanol was evaporated under reduced pressure and 118 ml of methylene chloride was added. The solution was purified by
10 acidic extraction (6.3 g of HCl (aqueous) in 24 ml of H₂O). The methylene chloride phase was treated with 3 g of sodium sulphate (anhydrous) in order to remove the residues of water. The solvent was evaporated and 85 ml of diisopropyl ether was added. The product was crystallized by cooling the solution to 0°C, isolated by filtration and washed with diisopropyl ether.

15 Yield: Approximately 85%

Claims

1. A method for the manufacture of felodipine, characterized by reacting 2,3-dichlorobenzylideneacetylacetic acid-methylester with ethyl 3-aminocrotonate in refluxing
5 alcohol in the presence of pyridine as catalyst.
2. A method according to claim 1 wherein the alcohol is ethanol.
3. A method according to any of claims 1-2 wherein the obtained felodipine is taken up
10 into a solution.
4. A method according to claim 3 wherein the obtained felodipine is taken up into ethyl acetate.
- 15 5. A method according to claim 3 wherein the obtained felodipine is taken up into methylene chloride.
6. A method according to any of claims 1-2 wherein the obtained felodipine is purified
20 by crystallization.
7. A method according to claim 6 wherein the crystallization is performed from acetone.
8. A method according to claim 6 wherein the crystallization is performed from
25 diisopropyl ether.
9. A method according to any of the preceding claims, wherein the amount of ethyl 3-aminocrotonate is 0.5-0.9 g per g of 2,3-dichlorobenzylideneacetylacetic acid-methylester.



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10. A method according to any of the preceding claims, wherein the amount of ethanol is 2.5-4.8 ml per g of 2,3-dichlorobenzylideneacetylacetic acid-methylester.
11. A method according to any of the preceding claims, wherein the amount of pyridine
5 is 0.03-0.2 ml per g of 2,3-dichlorobenzylideneacetylacetic acid-methylester.
12. A method for the manufacture of felodipine in the form of a pharmaceutical preparation wherein felodipine is produced according to any one of the preceding claims and thereafter purified felodipine is admixed with an excipient, diluent or carrier to provide
10 the pharmaceutical preparation.

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