(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
6 September 2002 (06.09.2002)

PCT

(10) International Publication Number
WO 02/067847 A2

(51) International Patent Classification[7]: A61K

(21) International Application Number: PCT/IB02/00638

(22) International Filing Date: 26 February 2002 (26.02.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
01/02572 26 February 2001 (26.02.2001) FR

(71) Applicant: **CLARIANT (FRANCE)** [FR/FR]; 70, Avenue du Général de Gaulle, F-92800 Puteaux (FR).

(72) Inventor: **SIDOT, Christian**; 12, Avenue de Landshut, F-60200 Compiegne (FR).

(74) Agent: **KACHHOLZ, Traudel**; Clariant International Ltd, Rothausstrasse 61, CH-4132 Muttenz 1 (CH).

(81) Designated States *(national)*: CN, IN, JP.

(84) Designated States *(regional)*: European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/067847 A2

(54) Title: PROCESS FOR THE PREPARATION OF ALKYL BENZOYLACRYLATES

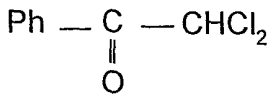
(57) Abstract: Process for the preparation of alkyl benzoylacrylates of formula (I) where R = alkyl, in which the reaction is carried out in an acid medium in the same reactor, without isolating the intermediate products, as follows: condensation of acetophenone with glyoxylic acid, elimination of a water/acetophenone mixture, elimination of the excess acetophenone, esterification with an alcohol in the presence of a strong acid, addition of a solvent, elimination of a mixture constituted by water, solvent and alcohol, dehydration by azeotropic distillation of the water, neutralization of the strong acid with a basic aqueous solution, decanting and concentration of the organic phase and recovery of the sought final product of formula (I).

PROCESS FOR THE PREPARATION OF ALKYL BENZOYLACRYLATES

The present invention relates to a process for the preparation of alkyl benzoylacrylates.

Alkyl benzoylacrylates and more particularly ethyl benzoylacrylate are useful products as intermediates in the pharmaceutical industry, and more particularly for the synthesis of Enalapril, an inhibitor of the angiotensin-converting enzyme.

Alkyl benzoylacrylates and more particularly ethyl benzoylacrylate can be prepared from benzoylacrylic acid, itself prepared from benzene and maleic anhydride (R. Delaby et al, Bull. Soc. Chim., 1961, p. 2061-64). They can also be prepared by reacting an alcoholate with



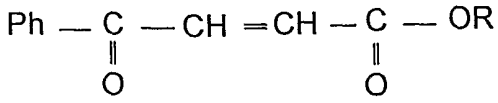
then reacting with triphenylcarbethoxymethylenephosphorane, and finally by sulphuric hydrolysis of the product obtained (C. Raulet and E. Levas, Bull. Soc. Chim. France, 1971, n°7, p. 2598-2606).

EP-A-0,494,620 describes the formation of aroylacrylic esters by reacting alkyl methyl ketones with acetal-esters or hemiacetal-esters of glyoxylic acid in a strong acid medium. These acetal-esters or hemiacetal-esters can be prepared in-situ in the reaction medium by reacting glyoxylic acid with an alcohol in a strong acid medium.

FR-A-2,504,127 describes the synthesis of trimethoxybenzoylacrylic acid or trimethoxybenzoyllactic acid by condensing glyoxylic acid or one of its alkyl esters with trimethoxyacetophenone.

More efficient processes for preparing alkyl benzoacrylates are always being sought.

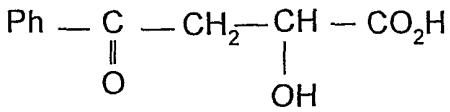
For this reason, a subject of the present invention is a process for the preparation of alkyl benzoylacrylates of formula (I)



(I)

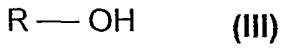
in which R is an alkyl group comprising 1 to 9 carbon atoms and Ph is a phenyl radical, characterized by the fact that the reaction is carried out in an acid medium, in the same reactor (so-called "one pot" reaction), without isolation of the intermediate products, by carrying out the following operations:

- condensation of acetophenone with glyoxylic acid in order to obtain a compound of formula (II)



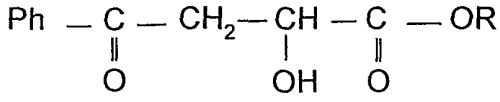
(II)

- elimination of a water/acetophenone mixture,
- elimination of the excess acetophenone,
- esterification of the compound of formula (II) with an alcohol of formula (III)



(III)

in which R is an alkyl group comprising 1 to 9 carbon atoms, in the presence of a strong acid, in order to obtain a compound of formula (IV)



(IV)

in which R and Ph have the same meaning as previously, without isolating the intermediate product,

- addition of a solvent,
- elimination of a mixture constituted by water, solvent and an alcohol of formula (III),
- dehydration of the compound of formula (IV) by azeotropic distillation of water,
- neutralization of the strong acid by a basic aqueous solution,

- decanting and concentration of the organic phase,
- recovery of the sought final product of formula (I).

R is a branched or preferably linear alkyl group. It preferably contains from 1 to 5 carbon atoms, and in particular from 1 to 3 carbon atoms. There can be mentioned for example the methyl, ethyl, n- and iso-propyl, n-, sec- and tert-butyl, n-pentyl radicals.

Under preferential conditions for the implementation of the above process, one or more of the following operations is carried out:

- 2 to 8 equivalents, and preferably 4 equivalents, of acetophenone are condensed with 1 equivalent of glyoxylic acid,
- the compound of formula (II) is esterified with 2 to 10 equivalents, preferably 3 equivalents, of an alcohol of formula (III) in the presence of a strong acid per equivalent of initial glyoxylic acid.

Under other preferential conditions of the invention

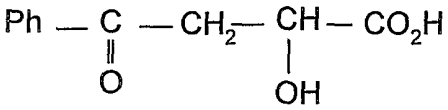
- the alcohol of formula III used is ethanol,
- the strong acid used is sulphuric acid,
- the azeotroping solvent is toluene,
- the ethyl benzoyllactate is dehydrated by azeotropic distillation after adding further toluene,
- the basic solution used is an aqueous solution of sodium bicarbonate.

Under other preferential implementation conditions, ethyl benzoylacrylate is prepared.

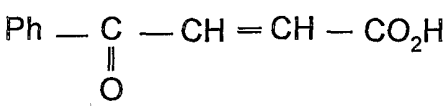
The process which is a subject of the present invention allows the direct preparation of alkyl benzoylacrylate starting from acetophenone and glyoxylic acid, without the intermediate isolation of benzoyllactic acid.

It is remarkably efficient in particular for the following reasons:

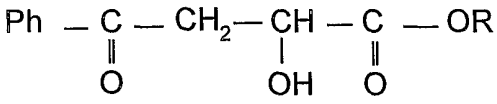
- the aldolization reaction between the acetophenone and the carbonyl function of the glyoxylic acid according to the invention produces benzoyllactic acid quantitatively



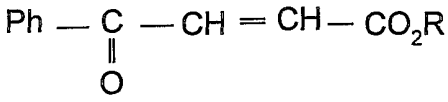
and the formation of the corresponding acrylic acid is minimized,



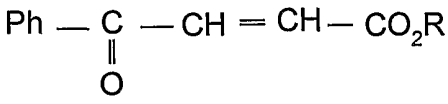
- the esterification of the benzoyllactic acid in the presence of an alcohol and a strong acid catalysis (sulphuric acid), initially, without elimination of the water formed, which allows the esterification of the benzoyllactic acid to alkyl benzoyllactate



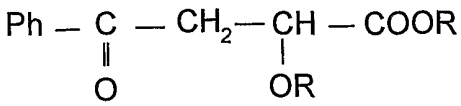
while avoiding dehydrating the alcohol function, which in turn avoids the formation of the compound of formula



- the dehydration of the benzoyllactic acid to alkyl benzoylacrylate of formula



minimizes the addition of alcohol on the double bond and avoids the formation of the by-product



This set of conditions leads in particular to an excellent yield.

The present invention also has the advantage of being able to recycle, if desired, the acetophenone introduced at the beginning of the reaction from the acetophenone-water mixture distilled during the reaction, which decants at ambient temperature.

The following examples will allow a better understanding of the invention.

EXAMPLE 1

The following are introduced into a reactor:

- 29.6 g of 50 % glyoxylic acid in water (0.2 mole),
- 96 g of acetophenone (0.8 mole). A heterogeneous reaction mixture is obtained the aqueous phase of which has an acid pH which is heated at 80°C under 50 millibars for 5 hours while eliminating 16.5 g of distillate comprising a water / acetophenone mixture 85/15.

The vacuum is then increased progressively to 2 millibars and the reaction medium is heated at 120°C for 8 hours in order to eliminate the excess acetophenone. The composition of the medium, determined by high performance liquid chromatography (HPLC), allows the determination of a yield of benzoyllactic acid of 92 % and of benzoylacrylic acid of 3 %. After returning to 70°C, the medium is diluted with 28 g of absolute ethanol (0.6 mole). The reaction medium is then heated under reflux for 2 hours in the presence of 0.34 g sulphuric acid. 75 g of toluene is then added and 40 g of a mixture of solvent constituted by water (10 %), toluene (45 %) and ethanol (45 %) is eliminated. Using HPLC analysis, it is noted that the reaction medium contains a great majority of ethyl benzoyllactate. Dehydration of the ethyl benzoyllactate to ethyl benzoylacrylate is carried out by azeotropic distillation of the water after adding 50 g of fresh toluene. 5.2 g of heavy phase is then eliminated constituted by 52 % water, 45 % ethanol and 3 % toluene. After neutralization of the sulphuric acid with an aqueous solution of sodium bicarbonate, decanting and concentration of the solvents, 44 g of a yellow oil is recovered containing 81 % ethyl benzoylacrylate (cis + trans), i.e. a yield of 87 % with respect to the starting glyoxylic acid.

EXAMPLE 2

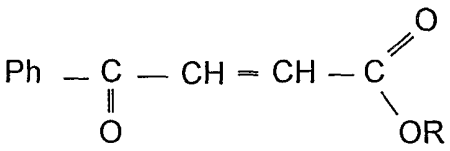
The following are introduced into a reactor:

- 593.2 g of 50 % glyoxylic acid in water (4 moles),
- 1,923 g of acetophenone (16 moles). A heterogeneous reaction mixture is obtained the aqueous phase of which has an acid pH, which is heated at 80°C under 50 millibars for 5 hours while eliminating 325.3 g of distillate comprising a water / acetophenone mixture 85/15.

The vacuum is then progressively increased to 2 millibars and the reaction medium is heated to 120°C for 8 hours in order to eliminate the excess acetophenone. The composition of the medium, determined by HPLC analysis, allows the determination of a yield of benzoyllactic acid of 89 % and of benzoylacrylic acid of 5 %. After returning to 70°C, the medium is diluted with 555.9 g of absolute ethanol (12 moles). The reaction medium is then heated under reflux for 2 hours in the presence of 7.1 g of sulphuric acid. 1501 g of toluene is then added and 796 g of a mixture of solvent constituted by water (9.1 %), toluene (45 %) and ethanol (46 %) is eliminated. Using HPLC analysis, it is noted that the reaction medium contains a great majority of ethyl benzoyllactate. Dehydration of the ethyl benzoyllactate to ethyl benzoylacrylate is carried out by azeotropic distillation of the water after adding 1213 g of fresh toluene. 110 g of heavy phase is then eliminated, constituted by approximately 50 % water and 50 % ethanol. After neutralization of the sulphuric acid using an aqueous solution of sodium bicarbonate, decanting and concentration of the solvents, 683 g of a yellow oil is recovered containing 98.9 % ethyl benzoylacrylate (cis + trans), i.e. a yield of 83 % with respect to the starting glyoxylic acid.

CLAIMS

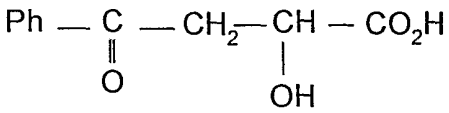
1. Process for the preparation of alkyl benzoylacrylates of formula



(I)

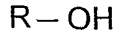
in which R is an alkyl group comprising 1 to 9 carbon atoms and Ph is a phenyl radical, characterized in that the reaction is carried out in an acid medium in the same reactor, without isolation of the intermediate products, by carrying out the following operations:

- condensation of the acetophenone with glyoxylic acid in order to obtain a compound of formula (II)



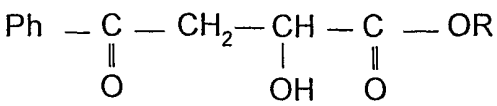
(II)

- elimination of a water/acetophenone mixture,
- elimination of the excess acetophenone,
- esterification of the compound of formula (II) with an alcohol of formula (III)



(III)

in which R is an alkyl group comprising 1 to 9 carbon atoms, in the presence of a strong acid, in order to obtain a compound of formula (IV)



(IV)

in which R and Ph have the same meaning as previously, without isolation of intermediate product,

- addition of a solvent,
- elimination of a mixture constituted by water, solvent and alcohol of formula (III),
- dehydration of the compound of formula (IV) by azeotropic distillation of the water,
- neutralization of the strong acid with a basic aqueous solution,
- decanting and concentration of the organic phase,
- recovery of the sought final product of formula (I).

2. Process according to claim 1, characterized by the fact that 1 equivalent of glyoxylic acid is reacted with 2 to 8 equivalents of acetophenone.

3. Process according to claim 1 or 2, characterized by the fact that 1 equivalent of glyoxylic acid is reacted with 4 equivalents of acetophenone.

4. Process according to one of claims 1 to 3, characterized by the fact that 2 to 10 equivalents of alcohol are reacted per equivalent of initial glyoxylic acid.

5. Process according to one of claims 1 to 4, characterized by the fact that 3 equivalents of alcohol are reacted per equivalent of initial glyoxylic acid.

6. Process according to one of claims 1 to 5, characterized by the fact that the alcohol of formula III used is ethanol.

7. Process according to one of claims 1 to 6, characterized by the fact that the strong acid used is sulphuric acid.

8. Process according to one of claims 1 to 7, characterized by the fact that the azeotroping solvent used is toluene.

9. Process according to one of claims 1 to 8, characterized by the fact that the basic aqueous solution used is an aqueous solution of sodium bicarbonate.

10. Process according to one of claims 1 to 9, characterized by the fact that ethyl benzoylacrylate is prepared.