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(54) Title: PROCESS FOR THE PREPARATION OF ESTERS OF 4-FLUOROSUBSTITUTED 3-OXO-ALCANOIC ACIDS

(57) Abstract: Esters of 4-fluorosubstituted 3-oxo-alcanoic acids can be prepared by addition reaction of ketene with the respective acid chloride, subsequent esterification and hydrodechlorination. Preferred reaction products are esters of 4,4- difluoro-3-oxo-butanioic acid.



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Process for the preparation of esters of 4-fluorosubstituted 3-oxo-alcanoic acids

The invention concerns a process for the preparation of esters of 4-fluorosubstituted 3-oxo-alcanoic acids by addition of fluorochloroalkyl carboxylic acid chlorides to ketene, esterification and hydrodechlorination. Specifically, the invention concerns a process for the preparation of esters of 4,4-difluoro-3-oxo-butanoic acid by addition of difluorochloroacetyl chloride to ketene, esterification and subsequent reduction.

Esters of 4,4-difluoro-3-oxo-butanoic acid, especially the ethyl ester, are building blocks in chemical synthesis. These esters are useful for preparing 3-difluoromethyl-4-pyrazole-carboxylic acid esters which are intermediates for the manufacture of pyrazole carboxanilide fungicides. The preparation of such fungicides is described in US patent 5,498,624 as cited in WO 2006/005612. Esters of 4,4-difluoro-3-oxo-butanoic acid are condensed with ethyl orthoformate and acetic anhydride, and the reaction product is reacted with methylhydrazine. The resulting pyrazole carboxylic acid ester is then further reacted to finally obtain the fungicide.

Esters of 4-fluorosubstituted 3-oxo-alcanoic acids, for example, 5,5,5-trifluoro-4-fluoro-3-oxo-pentanoic acid, are suitable as solvents.

Known methods to prepare esters of 4,4-difluoro-3-oxo-alcanoic acid are described in the following by the example of esters of 4,4-difluoro-3-oxo-butanoic acid. The methyl and ethyl esters of 4,4-difluoro-3-oxo-butanoic acid can be prepared by condensation with acetic acid esters under basic conditions. An alternative route is described in EP-A0 694526. Polyfluorocarboxylic acid chlorides or anhydrides are reacted with a carboxylic acid chloride in the presence of a tertiary amine, e.g. pyridine. Then, esterification is performed with an alcohol, for example, methanol or ethanol. Drawback is the low yield in case of difluoroacetoacetates.

Subject of the present invention is to provide a technically and economically advantageous process for the preparation of esters of 4-fluorosubstituted 3-oxo-alcanoic acids, and especially of esters of 4,4-difluoro-3-oxo-butanoic acid. This object is achieved by the process of the present invention.

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According to the broadest aspect of the present invention, esters of 4-fluorosubstituted 3-oxo-alcanoic acids are prepared by the reaction of compounds of formula (I)



- 5 wherein R is C₂F₅, CF₃ or F, with ketene forming an adduct, reaction of the adduct in an esterification step to form the respective ester, and subsequent hydrodechlorination to form a compound of formula (II)



- 10 wherein R has the meaning given above and R¹ is an alkyl group with 1 to 4 carbon atoms, or an alkyl group with 1 to 4 carbon atoms substituted by 1 or more fluorine atoms. Preferably, R¹ is methyl, ethyl or propyl.

- The invention will now be further explained in view of the most preferred aspect of the present invention, namely the preparation of esters of 4,4-difluoro-4-chloro-3-oxobutanoic acid from difluorochloroacetyl chloride – i.e. the compound of formula (I) wherein R is F - and ketene. According to this especially preferred process of the present invention, in an addition step, difluorochloroacetylchloride is reacted with ketene to form 4,4-difluoro-4-chloro-3-oxobutanoyl chloride which then is reacted in an esterification step into the respective 4,4-difluoro-4-chloro-3-oxo-butanoic acid ester which, in a reduction step, is reduced to form the respective ester of 4,4-difluoro-3-oxo-butanoic acid.

- The addition step can be performed in the gas phase or in the liquid phase. Preferably, the pressure is selected so that the gaseous ketene is introduced into the liquid difluorochloroacetyl chloride. The temperature is preferably in the range of -50 °C to +60 °C. Preferably, the pressure corresponds to the ambient pressure, but it can be higher than ambient pressure. Preferably, the pressure is equal to or lower than 5 bars (abs).

- The molar ratio between difluorochloroacetyl chloride and ketene preferably lies in a range from 1 : 0.95 to 1 : 2. If desired, even more ketene can be applied.

If desired, the addition reaction can be performed in an aprotic organic solvent, for example, in an aliphatic or aromatic hydrocarbon, or a halogenated hydrocarbon, e.g. in a chlorinated hydrocarbon.

- In one embodiment, the formed adduct is isolated from the reaction mixture, for example, by distillation, and the isolated product is then further

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reacted in the esterification step. In another embodiment, the reaction mixture is directly introduced into the esterification step without isolation of the adduct.

The esterification can be performed in any known manner. A very simple embodiment provides for the reaction of the acid chloride with the respective
5 alcohol in the absence or the presence of a base.

The esterification step is preferably performed in the liquid phase. Preferably, the pressure is equal to ambient pressure. It also may be above ambient pressure, e.g. up to 5 bars (abs).

The molar ratio between the acid chloride and the alcohol preferably lies in
10 a range from 1 : 0.8 to 1 : 1.5.

If desired, the addition reaction can be promoted by bases, for example, tertiary amines. If a base is added, it is advisable to cool the reaction mixture. Alternatively, the esterification can be performed in the presence of onium salts as described in US patents 6,525,213 and 5,405,991. The advantage of this kind
15 of reaction is that an ester phase may separate which makes isolation very easy. If no base is applied, it is advantageous to remove HCl which is a reaction product from the reaction mixture. This can be achieved by applying reduced pressure, passing inert gas through the reaction mixture, for example, nitrogen, argon or even dry air, or by heating the reaction mixture.

Finally, the CF₂Cl group is reduced to a CF₂H group. This can be achieved
20 y known methods. A very simple and preferred method is the reduction with metals, e.g. zinc. The reaction can be performed as described in WO 2005/085173. The chlorine-containing compound is reacted preferably with 0.9 to 2.1 equivalents of metallic zinc per chlorine atom to be substituted by a
25 hydrogen atom. An alcohol is present as proton source. Advantageously, the alcohol corresponds to the alcohol of the ester group of the butanoic acid ester. The alcohol may be present in excess and then serve as a solvent. If desired, other solvents may be present, for example, aprotic organic solvents, for example, the ester of the alcanoic acid produced in an earlier batch, or, in this
30 preferred embodiment, respective esters of 4,4-difluoro-4-chloro-3-oxobutanoic acid produced in an earlier batch.

The difluorochloroacetyl chloride which is applied in the addition step is a commercial product. A preferred method to produce it comprises a step of
photochemical oxidation of 1,1-difluoro-1,2,2-trichloroethane with oxygen in the
35 presence or absence of promoters of the reaction, for example, chlorine. According to US patent 5,545,298, the photo oxidation can be performed in the

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absence of chlorine under irradiation through quartz glass. If desired, the reaction can be performed without pressurization. According to US patent 5,569,782 photo oxidation is performed in the absence of chlorine under exposure with light of a wavelength equal to or shorter than 290 nm. The undesired wavelengths can be cut off by applying borosilicate glass. Alternatively, radiation sources could be applied which emit radiation essentially only in the desired range. If desired, the oxidation reaction could be performed under unpressurized conditions. The reaction can also be performed under pressure. Fluorinated carboxylic acid chlorides which are alpha-substituted by a chlorine atom can be prepared analogously from respective starting compounds.

The chlorofluorosubstituted starting compounds needed for the photo oxidation reaction can be prepared according to known methods. For example, 1,1,-difluoro-1,2,2-dichloroethane is commercially available; it can be prepared by the reaction of tetrachloroethylene and HF in the presence of catalysts, e.g. tantalum halides or antimony halides, especially antimony (V) chloride or its fluorination products.

The method according to the present invention provides a cheap, technically feasible process for the preparation of esters of 4,4-difluoro-3-oxo-butanoic acid and its homologues.

The following example is intended to further explain the invention without limiting it.

Example: Preparation of esters of 4,4-difluoro-3-oxo-butanoic acid
1,1,-difluoro-1,2,2-trichloroethane from a commercial source is reacted with oxygen in the absence of chlorine in an apparatus with borosilicate glass as filter for light with a wavelength of lower than around 290 nm under the conditions indicated in US 5,569,782.

HCl is removed, and without separate isolation of the formed chlorodifluoroacetyl chloride, the reaction product is reacted with ketene by passing ketene through the liquid acid chloride, dissolved in methylene chloride. The reaction mixture is cooled and kept in a range of -10 to -30 °C. Afterwards, lightboiling substances are removed, and the raw difluorochloroacetylacetic acid chloride is esterified with ethanol in the absence of a base. HCl is removed, and the resulting raw product is reacted with zinc powder in the presence of ethanol as described in WO 2005/085173. The resulting ethyl ester of 4,4-difluoro-3-oxo-butanoic acid is isolated by distillation.

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CLAIMS

1. Process for the preparation of esters of 4-fluorosubstituted 3-oxo-alcanoic acids by the reaction of compounds of formula (I)



- 5 wherein R is C₂F₅, CF₃ or F, with ketene forming an adduct, reaction of the adduct in an esterification step to form the respective ester, and subsequent hydrodechlorination to form a compound of formula (II)



- 10 wherein R has the meaning given above and R¹ is an alkyl group with 1 to 4 carbon atoms, an alkyl group with 1 to 4 carbon atoms substituted by 1 or more fluorine atoms.

2. Process according to claim 1 wherein R is F.

3. Process according to claim 1 or 2 wherein R¹ is methyl, ethyl or propyl, preferably ethyl.

- 15 4. Process according to claim 1 wherein the esterification step is performed in the absence of a base or phase-separating agents.

5. Process according to claim 1 wherein the compound RCFCIC(O)Cl is prepared by photo oxidation of RCFCICHCl₂ with oxygen wherein R has the meaning given above.

- 20 6. Process according to claim 1 wherein the hydrodechlorination is performed by reaction of the ester with zinc in the presence of the alcohol applied in the esterification step.

INTERNATIONAL SEARCH REPORT

International application No

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A. CLASSIFICATION OF SUBJECT MATTER

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C07C59/21

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2005/003077 A (BAYER CROPSCIENCE AG [DE]; GALLENKAMP BERND [DE]; MULDER LUBBERTUS [DE]) 13 January 2005 (2005-01-13) page 1, line 26 - page 3, line 4 page 3, last paragraph page 4, line 15 - line 26 page 9, line 29 - line 32 examples 1,2	1-6
Y	DE 11 58 490 B (HOECHST AG) 5 December 1963 (1963-12-05) column 1, line 29 - column 2, line 31 column 3, line 32 - line 37 example 4	1-6
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Further documents are listed in the continuation of Box C.



See patent family annex.

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T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 545 298 A (BRAUN, MAX [DE] ET AL) 13 August 1996 (1996-08-13) cited in the application example 1	5
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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