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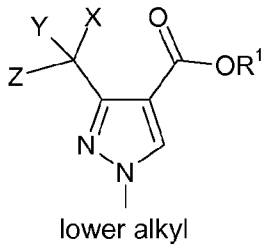
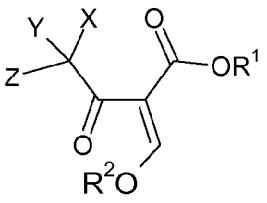
(54) **Title**: PROCESS FOR PREPARING 1,3-DISUBSTITUTED PYRAZOLECARBOXYLIC ESTERS

(57) **Abstract**: A process for preparing 1,3-disubstituted pyrazolecarboxylic esters of the formula (I); where X, Y, Z = hydrogen or halogen and R^1 = C_1-C_6-alkyl, by metering an enol ether of the formula (III); where R^2 is C_1-C_6-alkyl at from (-41) to (-8O)°C into an alkyl hydrazine of the formula II H_2N-NH-lower alkyl (II).



(I)

H_2N-NH-lower alkyl (II)



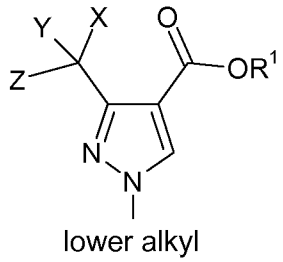
(III)

WO 2010/009990 A1

Process for preparing 1,3-disubstituted pyrazolecarboxylic esters

Description

The present invention relates to a process for preparing 1,3-disubstituted pyrazolecarboxylic esters of the formula (I)



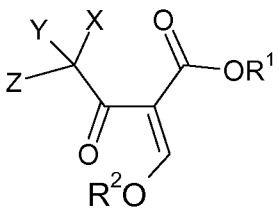
(I)

where

X, Y, Z are each hydrogen or halogen and

R^1 is C_1-C_6-alkyl,

which comprises metering an enol ether of the formula III



(III)

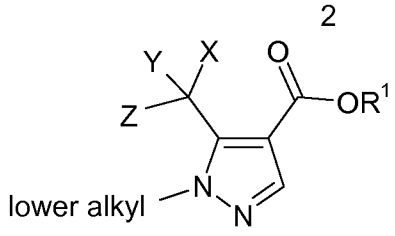
where R^2 is C_1-C_6-alkyl at from (-41) to (-80)°C into an alkyl hydrazine of the formula II

H_2N-NH-lower alkyl (II).

Typically, the pyrazole ester synthesis is effected within the temperature range from +25 to (-15)°C (cf., for example, WO 2005/003077, US 5,498,624, US 5,093,347, JP-A 2000/212166, WO 2006/090778, JP 01113371).

In addition, WO 2005/123690 (see preparation example) describes the synthesis of ethyl 3-difluoromethyl-1-methyl-1H-pyrazole-4-carboxylate at (-40)°C.

In the syntheses known to date for preparing 1,3-disubstituted pyrazole-4-carboxylic esters, more than 10% of the isomeric 1,5-disubstituted pyrazole-4-carboxylic acid derivatives VI is always also obtained



(VI)

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The purification of the products of value I (i.e. the removal of the isomer VI) is found to be very complicated and the yields are accordingly low.

It was accordingly an object of the invention to provide a process usable on the industrial scale for substantially isomerically pure preparation of the 1,3-disubstituted pyrazolecarboxylic esters I.

Accordingly, it has been found that the 1,3-disubstituted pyrazolecarboxylic esters I are obtainable in high yields and with an isomeric purity of more than 6.5:1, by metering an enol ether III into an alkyl hydrazine II at from (-41) to (-80)°C.

The alkyl hydrazines II are commercially available. They can be used in pure form or as an aqueous solution (e.g. 35%). However, even greater amounts of water should be avoided, since the isomer ratio otherwise worsens again.

The enol ethers III are generally obtainable according to WO 2005/003077.

The term “halogen” denotes in each case fluorine, chlorine, bromine or iodine, preferably fluorine or chlorine.

“Lower alkyl” represents methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl and 1,1-dimethylethyl, especially methyl.

”C_1-C_6-Alkyl”, as used herein, denotes a saturated, straight-chain or branched hydrocarbon group comprising from 1 to 6 carbon atoms, especially from 1 to 4 carbon atoms, for example methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl and isomers thereof. C_1-C_4-Alkyl comprises, for example, methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl.

The preparation of ethyl 3-difluoromethyl-1-methyl-1H-pyrazole-4-carboxylate is very particularly preferred.

According to the invention, the reaction is conducted at from (-41) to (-80)°C, especially at from (-50) to (-60)°C.

The alkyl hydrazine II is advantageously cooled to the reaction temperature in a solvent or diluent and then the enol ether III is metered in. The reverse metering sequence generally affords significantly poorer isomeric ratios.
The enol ether III is preferably used in undiluted form or dissolved in the organic solvent in which (II) has also been initially charged. The metered addition of III is generally effected over the course of from 0.58 to 20 hours, especially from 2 to 10 hours.

The alkyl hydrazines II can be used in pure form or as an aqueous solution (e.g. 35%). However, even greater amounts of water should be avoided, since the isomer ratio otherwise worsens again.

Usable solvents are lower alcohols, especially ethanol. For reasons of stability, it is advisable to freshly prepare the solution of enol ether III and the alcohol used only shortly before the metered addition.
In the case of metering times of more than 2 hours, the undiluted metered addition of III is advantageous.

Enol ether I and alkyl hydrazine II are typically used in about equimolar amounts, but it is also possible to use one component in a small excess, up to about 30 mol%.

Advantageously, the alkyl hydrazine is used in excess; preference is given to 1.05-1.3 molar equivalents.

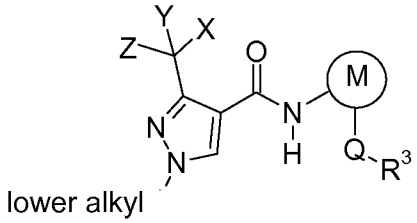
It is normal to work at atmospheric pressure or under the autogenous pressure of the reaction mixture.

The pyrazole-4-carboxylic esters I formed can be purified in a customary manner (e.g. distillation, crystallization, etc), or be converted further as crude products (if appropriate dissolved in a solvent).

In a preferred embodiment of the process, the crude pyrazole ester solution without intermediate purification is hydrolyzed to the pyrazole carboxylic acid IV, for example according to WO 2005/123690 or US 5,498,624. Only at the acid stage is the 1,3-disubstituted pyrazole-4-carboxylic acid IV purified and isolated by precipitation and

filtration.

The 1,3-disubstituted pyrazole-4-carboxylic esters I and 1,3-disubstituted pyrazole-4-carboxylic acids IV are valuable active ingredients in crop protection. They serve, for example, to prepare pyrazolylcarboxamides of the formula V



(V)

where the substituents are each defined as follows:

M is thienyl or phenyl which may bear a halogen substituent;

Q is a direct bond, cyclopropylene, or a fused bicyclo[2.2.1]heptane-or bicyclo[2.2.1]heptene ring;

R^3 is hydrogen, halogen, C_1-C_6-alkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, mono- to trisubstituted phenyl, where the substituents are each independently selected from halogen and trifluoromethylthio, or cyclopropyl.

Preferred arylcarboxamides V are penthiopyrad, bixafen, N-(3',4',5'-trifluorobiphenyl-2-yl)-3-difluoromethyl-1-methylpyrazole-4-yl-carboxamide, N-(2-bicyclopropyl-2-ylphenyl)-3-difluoromethyl-1-methylpyrazol-4-yl-carboxamide (common name: sedaxane) and 3-(difluoromethyl)-1-methyl-N-[1,2,3,4-tetrahydro-9-(1-methylethyl)-1,4-methanonaphthalen-5-yl]-1H-pyrazol-4-yl-carboxamide (common name: isopyrazam).

Preparation examples:

Example 1 (inventive)
Preparation of ethyl 3-difluoromethyl-1-methyl-1H-pyrazole-4-carboxylate at (-60)°C and subsequent hydrolysis to 3-difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid.

43.8 g (0.33 mol) of methylhydrazine solution (34.7% by weight of methylhydrazine in water) and 270 g of ethanol (anhydrous, undenatured) were initially charged and cooled to (-60)°C. Within 2 hours, at (-60)°C, a freshly prepared solution of 71.1 g (0.3 mol) of ethyl 2-ethoxymethylene-4,4-difluoro-3-oxobutyrate (93.7%) in 71 g of ethanol was added dropwise. This formed a suspension which was stirred at (-60)°C for another hour and then warmed to 25-30°C within 3 hours. The solution comprised

11.18% by weight of the desired ethyl 3-difluoromethyl 1-methyl-1H-pyrazole-4-carboxylate and only 1.14% by weight of the undesired isomeric ethyl 5-difluoromethyl-1-methyl-1H-pyrazole-4-carboxylate (HPLC analysis, quantification with external standard). The isomer ratio was 9.8 : 1.

252.5 g (0.45 mol) of 10% aqueous potassium hydroxide solution were metered and the reaction mixture was stirred at 60°C for 3 hours. The solvent was then distilled off completely under reduced pressure and the remaining residue dissolved in 480 g of demineralized water. 100 g (0.877 mol) of conc. hydrochloric acid (32%) were added dropwise to the salt solution at 55°C within 20 minutes, in the course of which the desired carboxylic acid crystallized out. The suspension was cooled to 3°C and stirred at this temperature for a further 1 hour. The solid was filtered off and washed twice with 100 g of cold demineralized water (3°C). After the drying (60°C, 20 mbar), 45.1 g of 3-difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid were obtained in a purity of 98.6% by weight. The yield, based on the molar amount of ethyl 2-ethoxymethylene-4,4-difluoro-3-oxobutyrate used, was 84.2%.

Example 2 (comparative example)
Preparation of ethyl 3-difluoromethyl-1-methyl-1H-pyrazole-4-carboxylate at (-40)°C and subsequent hydrolysis to 3-difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid

43.8 g (0.33 mol) of methylhydrazine solution (34.7% by weight of methylhydrazine in water) and 270 g of ethanol (anhydrous, undenatured) were initially charged and cooled to (-40)°C. Within 2 hours, at (-40)°C, a freshly prepared solution of 71.1 g (0.3 mol) of ethyl 2-ethoxymethylene-4,4-difluoro-3-oxobutyrate (93.7%) in 71 g of ethanol was added dropwise. This formed a suspension which was stirred at (-40)°C for another hour and then warmed to 25-30°C within 1 hour. The solution comprised 10.45% by weight of the desired ethyl 3-difluoromethyl 1-methyl-1H-pyrazole-4-carboxylate and 1.6% by weight of the undesired isomeric ethyl 5-difluoromethyl-1-methyl-1H-pyrazole-4-carboxylate (HPLC analysis, quantification with external standard). The isomer ratio was 6.5 : 1.

252.5 g (0.45 mol) of 10% aqueous potassium hydroxide solution were metered and the reaction mixture was stirred at 60°C for 3 hours. The solvent was then distilled off completely under reduced pressure and the remaining residue dissolved in 480 g of demineralized water. 100 g (0.877 mol) of conc. hydrochloric acid (32%) were added dropwise to the salt solution at 55°C within 20 minutes, in the course of which the desired carboxylic acid crystallized out. The suspension was cooled to 3°C and stirred at this temperature for a further 1 hour. The solid was filtered off and washed twice with 100 g of cold demineralized water (3°C). After the drying (60°C, 20 mbar), 42.5 g of 3-difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid were obtained in a purity of 98.7% by weight. The yield, based on the molar amount of ethyl 2-ethoxymethylene-4,4-difluoro-3-oxobutyrate used, was 79.4%.

Example 3 (comparative example)
Preparation of ethyl 3-difluoromethyl-1-methyl-1H-pyrazole-4-carboxylate at (-20)°C and subsequent hydrolysis to 3-difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid

43.8 g (0.33 mol) of methylhydrazine solution (34.7% by weight of methylhydrazine in water) and 270 g of ethanol (anhydrous, undenatured) were initially charged and cooled to (-20)°C. Within 2 hours, at (-20)°C, a freshly prepared solution of 71.1 g (0.3 mol) of ethyl 2-ethoxymethylene-4,4-difluoro-3-oxobutyrate (93.7%) in 71 g of ethanol was added dropwise. This formed a suspension which was stirred at (-20)°C for another hour and then warmed to 25-30°C within 1 hour. The solution comprised 10.05% by weight of the desired ethyl 3-difluoromethyl 1-methyl-1H-pyrazole-4-carboxylate and 2.27% by weight of the undesired isomeric ethyl 5-difluoromethyl-1-methyl-1H-pyrazole-4-carboxylate (HPLC analysis, quantification with external standard). The isomer ratio was 4.4 : 1.
252.5 g (0.45 mol) of 10% aqueous potassium hydroxide solution were metered and the reaction mixture was stirred at 60°C for 3 hours. The solvent was then distilled off completely under reduced pressure and the remaining residue dissolved in 480 g of demineralized water. 100 g (0.877 mol) of conc. hydrochloric acid (32%) were added dropwise to the salt solution at 55°C within 20 minutes, in the course of which the desired carboxylic acid precipitated out. The suspension was cooled to 3°C and stirred at this temperature for a further 1 hour. The solid was filtered off and washed twice with 100 g of cold demineralized water (3°C). After the drying (60°C, 20 mbar), 42.3 g of 3-difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid were obtained in a purity of 95.0% by weight (4.06% by weight of incorrect isomer). The yield, based on the molar amount of ethyl 2-ethoxymethylene-4,4-difluoro-3-oxobutyrate used, was 76.1%.

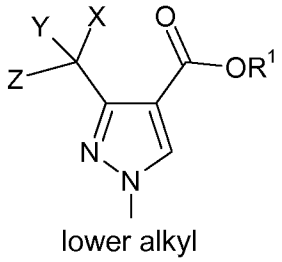
Example 4 (inventive)
Preparation of ethyl 3-difluoromethyl-1-methyl-1H-pyrazole-4-carboxylate at from (-50) to (-60)°C and subsequent hydrolysis to 3-difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid

A 400 liter stirred vessel was initially charged with 22.6 kg (172 mol) of methylhydrazine solution (35% by weight of methylhydrazine in water) and 132 kg of ethanol, and cooled to (-55)°C. Within 2.33 hours, at internal temperature from (-50) to (-60)°C, 40.4 kg (172.5 mol) of ethyl 2-ethoxymethylene-4,4-difluoro-3-oxobutyrate (94.8%) were metered in from a reservoir vessel. The reservoir vessel was rinsed out with 9.1 kg of ethanol. The suspension was stirred at (-55)°C for a further one hour and then the vessel contents were heated to 25°C within 4 hours. 102.3 kg (255.75 mol) of 10% sodium hydroxide solution were metered in within 45 minutes, the feed line was rinsed out with 10 liters of demineralized water and the reaction mixture was stirred at

60°C for 3 hours. After cooling to 25°C, the pressure was reduced stepwise down to 50 mbar. In the course of slow heating to internal temperature 42°C, a total of 180 liters of ethanol/water were distilled off. 300 liters of water were fed and the reaction mixture was cooled to 10°C. At this temperature, 47.8 kg (419 mol) of hydrochloric acid (32%) were metered in within one hour. After the feed line had been rinsed with 10 liters of water, the resulting suspension was stirred at 25°C for 12 hours. The solids were then filtered off in portions through a pressure filter and the filtercake was washed with 30 liters of demineralized water (with stirring). The solids were substantially freed of liquid by injecting 2.5 bar of nitrogen and, after discharge, dried in a drying cabinet (35-40°C, 25 mbar). After drying, 25.1 kg of 3-difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid were obtained in a purity of 99.6% (GC area%). The yield, based on the molar amount of methylhydrazine used, was 82.6%.

Claims

1. A process for preparing 1,3-disubstituted pyrazolecarboxylic esters of the formula I



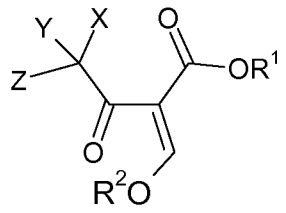
(I)

where

X, Y, Z are each hydrogen or halogen and

R^1 is C_1-C_6-alkyl,

which comprises metering an enol ether of the formula III



(III)

where R^2 is C_1-C_6-alkyl at from (-41) to (-80)°C into an alkyl hydrazine of the formula II

H_2N-NH-lower alkyl (II).

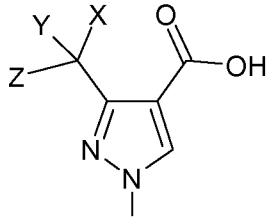
2. The process according to claim 1, wherein X and Y are each fluorine or chlorine and Z is hydrogen.

3. The process according to either of the preceding claims, wherein the reaction of II with III is undertaken in a lower alcohol.

4. The process according to any one of the preceding claims, wherein from 1.05 to 1.3 molar equivalents of alkyl hydrazine II, based on the amount of enol ether III, are used.

5. The process according to any one of the preceding claims, wherein the reaction of II with III is undertaken at from (-50) to (-60)°C.

6. A process for preparing 1,3-disubstituted pyrazolecarboxylic acids of the formula IV



(IV) ,

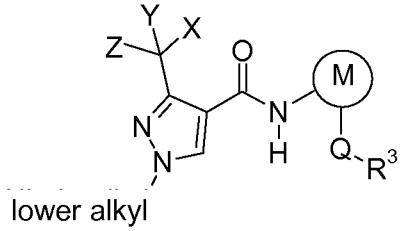
where X, Y and Z are each as defined in claim 1, which comprises

a) preparing a 1,3-disubstituted pyrazolecarboxylic ester of the formula I according to claim 1 and

b) converting the compound I to the compound IV.

7. The use of 1,3-disubstituted pyrazolecarboxylic esters of the formula I, obtained according to claim 1, to prepare 1,3-disubstituted pyrazolecarboxylic acids of the formula IV according to claim 6.

8. The use of 1,3-disubstituted pyrazolecarboxylic esters of the formula I, obtained according to claim 1, to prepare pyrazolylcarboxamides of the formula V



(V)

where the substituents are each defined as follows:

M is thienyl or phenyl which may bear a halogen substituent;

Q is a direct bond, cyclopropylene, or a fused bicyclo[2.2.1]heptane-or bicyclo[2.2.1]heptene ring;

R^3 is hydrogen, halogen, C_1-C_6-alkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, cyclopropyl or mono- to trisubstituted phenyl, where the substituents are each independently selected from halogen and trifluoromethylthio.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/058854

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D233/90

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)
C07D

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, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/123690 A (BASF AG [DE]; GEWEHR MARKUS [DE]; MUELLER BERND [DE]; GROTE THOMAS [DE]) 29 December 2005 (2005-12-29) cited in the application	1-4,6-8
A	page 21, line 20 - page 21, line 25	5
A	EP 1 854 788 A (SAGAMI CHEM RES [JP]; JAPAN FINECHEM COMPANY INC [JP]) 14 November 2007 (2007-11-14) cited in the application examples 1-28	1-8
A	US 5 093 347 A (GRANETO MATTHEW J [US] ET AL) 3 March 1992 (1992-03-03) cited in the application example 1	1-8

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
9 September 2009	16/09/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Usuelli, Ambrogio

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2009/058854

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