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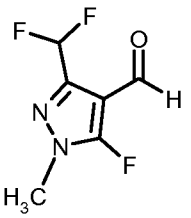
(54) Title: PROCESS FOR PREPARING 5-FLUORO-1-METHYL-3-DIFLUOROMETHYL-1H-PYRAZOLE-4-CARBALDEHYDE

(57) Abstract: The present invention relates to a novel process for preparing 5-fluoro-1-methyl-3-difluoromethyl-1H-pyrazole-4-carbaldehyde, a useful intermediate in the manufacture of fungicides.

Process for preparing 5-fluoro-1-methyl-3-difluoromethyl-1H-pyrazole-4-carbaldehyde

The present invention relates to a novel process for preparing 5-fluoro-1-methyl-3-difluoromethyl-1H-pyrazole-4-carbaldehyde (I), a useful intermediate in the manufacture of fungicides.

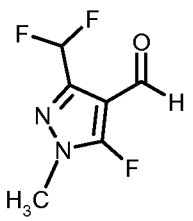


(I)

Processes for exchanging chlorine for fluorine (halex processes) are known particularly for 5-chloro-1,3-dialkyl-1H-pyrazole-4-carbonyl chlorides (cf. for example WO 2007/031212 and EP-A 0 776 889). It is also known from WO 2011/061205 that 5-fluoro-1-alkyl-3-fluoroalkyl-1H-pyrazole-4-carbonyl chlorides can be prepared by reacting in a first step 5-chloro-1-alkyl-3-fluoroalkyl-1H-pyrazole-4-carbaldehyde with metal fluorides like KF as fluorinating reagent to obtain 5-fluoro-1-alkyl-3-fluoroalkyl-1H-pyrazole-4-carbaldehyde , followed by a second reaction with a chlorinating agent to obtain the acyl chloride derivatives.

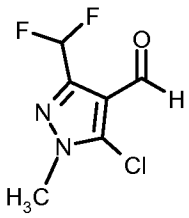
It has now been found that the fluorination occurring in the preparation of 5-fluoro-1-methyl-3-difluoromethyl-1H-pyrazole-4-carbaldehyde from 5-chloro-1-methyl-3-difluoromethyl-1H-pyrazole-4-carbaldehyde can be significantly and surprisingly accelerated and improved by the utilization of a phase transfer catalysts selected among tetrabutylammonium chloride, bromide or hydrogen sulphate in dimethylformamide or dimethylacetamide as solvent. Under such conditions, it is possible to reduce both the reaction time and the amount of potassium fluoride used for the fluorination, leading to a cheaper and more sustainable process.

The present invention relates to a process for preparing 5-fluoro-1-methyl-3-difluoromethyl-1H-pyrazole-4-carbaldehyde of formula (I)



(I)

characterized in that 5-chloro-3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carbaldehyde of formula (II)



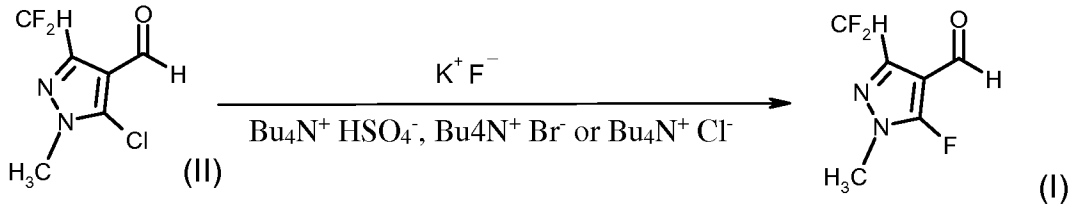
(II)

is reacted with potassium fluoride of formula (III)

$K^+ F^-$ (III)

in the presence of a phase transfer catalyst selected among tetrabutylammonium chloride, bromide or hydrogen sulphate, preferably tetrabutylammonium hydrogen sulphate, in dimethylformamide or dimethylacetamide as solvent.

The process according to the invention can be illustrated by the following formula scheme:



where the fluorination is performed with potassium fluoride in the presence of a phase transfer catalyst selected among tetrabutylammonium chlorid, bromid or hydrogen sulphate, preferably tetrabutylammonium hydrogen sulphate, in dimethylformamide or dimethylacetamide as solvent.

5-Chloro-1-alkyl-3-fluoroalkyl-1H-pyrazole-4-carbaldehydes are known or obtainable by known methods (cf. *J. Het. Chem.* **1990**, *27*, 243, WO 2006/018725).

5-Chloro-1-alkyl-3-difluoroalkyl-1H-pyrazole-4-carbaldehyde of formula (II) can be be prepared according to WO 2011/061205.

Potassium fluoride is a known synthesis chemical.

Reaction temperature in the process according to the invention is from 130°C to 160°C, preferably from 145°C to 155°C.

Reaction time is from 2 to 4 hours, preferably 3 hours.

The process according to the invention is carried out by using generally from 1 to 1.5 mol, preferably from 1.1 to 1.5 mol, of potassium fluoride per mole of 5-chloro-1-methyl-3-difluoromethyl-1H-pyrazole-4-carbaldehyde of formula (II).

The process according to the invention is carried out by using generally from 1 to 5 mol % of the phase transfer catalyst per mole of 5-chloro-1-methyl-3-difluoromethyl-1H-pyrazole-4-carbaldehyde of formula (II).

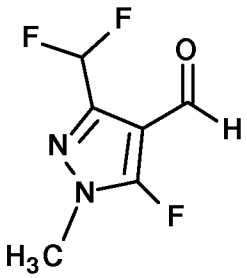
The process is preferably performed in equipment which is not a glass equipment, because KF can react under the reaction conditions with the glass equipment to produce side products (H_2O). Teflon or stainless steel equipment is preferable.

The process can be performed under normal atmosphere or under pressure (in closed vessel).

The potassium fluoride is generally used as a spray-dried.

Preparation examples

Example 1: preparation of 5-fluoro-1-methyl-3-difluoromethyl-1H-pyrazole-4-carbaldehyde (I) in presence of the catalyst $Bu4N^+$ $HSO4^-$ in dimethylacetamide



(I)

19.4 g (100 mmol) of 5-chloro-1-methyl-3-difluoromethyl-1H-pyrazole-4-carbaldehyde (II) were initially charged in 120 ml dimethylacetamide. This was followed by the addition of 6,84 g (120 mmol) of spry dried potassium fluoride and 1 g (3 mol %) of $Bu4N^+$ $HSO4^-$, heating to 150°C and subsequent stirring at that temperature for 3 hours. GC (gas chromatography) of the reaction mixture shows 100 % conversion This was followed by dilution of the mixture with toluene, filtration and removal of the solvent in vacuo at 1 mbar and 70°C to obtain 18,5 g of 5-fluoro-1-methyl-3-difluoromethyl-1H-pyrazole-4-carbaldehyde having a purity w.w. % of 90 .

^1H NMR (CD_3CN): δ = 9.8 (1H, s), 6.88 (1H, t), 3.7 (3H, s) ppm.
^{19}F NMR (CD_3CN): δ = −114.75 (2F, t), -124.06 (1F, s) ppm.

Example 2: the reaction was performed similar to example 1 but without the catalyst $Bu4N^+$ $HSO4^-$. In these conditions, GC of the reaction mixture shows 55% of conversion after 3 hours, 65% of conversion after 6 hours, 75% of conversion after 9 hours and 78% of conversion after 15h.

Example 3 : preparation of 5-fluoro-1-methyl-3-difluoromethyl-1H-pyrazole-4-carbaldehyde (I) in presence of the catalyst $Bu4N^+$ $HSO4^-$ in dimethylformamide.

19.4 g (100 mmol) of 5-chloro-1-methyl-3-difluoromethyl-1H-pyrazole-4-carbaldehyde (II-1) were initially charged in 120 ml dimethylformamide. This was followed by the addition of 6,84 g (120 mmol) of spry dried potassium fluoride and 1 g (3 mol %) of $Bu4N^+$ $HSO4^-$, heating to 150°C and subsequent stirring at that temperature for 3 hours. GC of the reaction mixture shows 100 % conversion. This was followed by dilution of the mixture with toluene, filtration and removal of the solvent in vacuo at 0.5 mbar and 70°C to obtain 18,3 g of 5-fluoro-1-methyl-3-difluoromethyl-1H-pyrazole-4-carbaldehyde having a purity w.w. % of 92.

Example 4: The reaction was performed similar to example 3, but without the catalyst $Bu4N^+$ $HSO4^-$. In these conditions, GC of the reaction mixture shows 52% of conversion after 3 hours, 73% of conversion after 6 hours, 83% of conversion after 9 hours and 93% of conversion after 15h.

Example 5. preparation of 5-fluoro-1-methyl-3-difluoromethyl-1H-pyrazole-4-carbaldehyde (I) in presence of the catalyst $Bu4N^+$ $HSO4^-$ in dimethylformamide.

19.4 g (100 mmol) of 5-chloro-1-methyl-3-difluoromethyl-1H-pyrazole-4-carbaldehyde (II-1) were initially charged in 120 ml dimethylformamide. This was followed by the addition of 6,27 g (110 mmol) of spry dried potassium fluoride and 1 g (3 mol %) of $Bu4N^+$ $HSO4^-$, heating to 150°C and subsequent stirring at that temperature for 3 hours. GC of the reaction mixture shows 99 % conversion. This was followed by dilution of the mixture with toluene, filtration and removal of the solvent in vacuo at 1 mbar and 70°C to obtain 18,1g of 5-fluoro-1-methyl-3-difluoromethyl-1H-pyrazole-4-carbaldehyde having a purity w.w. % of 89.

Example 6 : The reaction was performed similar to experiment 5, but without the catalyst $Bu4N^+$ $HSO4^-$. In these conditions, GC of the reaction mixture shows 35% of conversion after 3 hours, 50% of conversion after 6 hours, and 65% of conversion after 15h.

Example 7 : preparation of 5-fluoro-1-methyl-3-difluoromethyl-1H-pyrazole-4-carbaldehyde (I) in presence of the catalyst $Bu4N^+$ Br^- in dimethylformamide

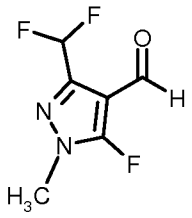
19.4 g (100 mmol) of 5-chloro-1-methyl-3-difluoromethyl-1H-pyrazole-4-carbaldehyde (II-1) were initially charged in 120 ml dimethylformamide. This was followed by the addition of 6,27 g (110 mmol) of spry dried potassium fluoride and 0,96 g (3 mol %) of $Bu4N^+$ Br^-, heating to 150°C and subsequent stirring at that temperature for 3 hours. GC of the reaction mixture shows 98 % conversion. This was followed by dilution of the mixture with toluene, filtration and removal of the solvent in vacuo at 0.5 mbar and 70°C to obtain 17,8 g of 5-fluoro-1-methyl-3-difluoromethyl-1H-pyrazole-4-carbaldehyde having a purity w.w. % of 89.

Example 8 : preparation of 5-fluoro-1-methyl-3-difluoromethyl-1H-pyrazole-4-carbaldehyde (I) in dimethylacetamide

19.4 g (100 mmol) of 5-chloro-1-methyl-3-difluoromethyl-1H-pyrazole-4-carbaldehyde (II-1) were initially charged in 120 ml dimethylacetamide. This was followed by the addition of 8,55 g (150 mmol) of spry dried potassium fluoride, heating to 150°C and subsequent stirring at that temperature for 3 hours. GC shows only 55 % conversion.

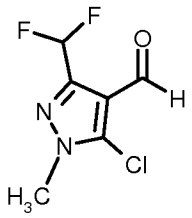
Claims:

1. Process for preparing 5-fluoro-1-methyl-3-difluoromethyl-1H-pyrazole-4-carbaldehyde of formula (I)



(I)

characterized in that 5-chloro-3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carbaldehyde of formula (II)



(II)

is reacted with potassium fluoride of formula (III)

$K^+ F^-$ (III)

in the presence of a phase transfer catalyst selected among tetrabutylammonium chloride, bromide or hydrogen sulphate in dimethylformamide or dimethylacetamide as solvent.

2. Process according to claim 1 wherein the phase transfer catalyst is tetrabutylammonium hydrogen sulphate.

3. Process according to claim 1 or 2 wherein the reaction temperature is from 130°C to 160°C.

4. Process according to anyone of claims 1 to 3 wherein the reaction time is from 2 to 4 hours.

5. Process according to anyone of claims 1 to 4 wherein from 1 to 1.5 mol of potassium fluoride per mole of 5-chloro-1-methyl-3-difluoromethyl-1H-pyrazole-4-carbaldehyde of formula (II) is used.

6. Process according to anyone of claims 1 to 5 wherein from 1 to 5 mol % of the catalyst per mole of 5-chloro-1-methyl-3-difluoromethyl-1H-pyrazole-4-carbaldehyde of formula (II) is used.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/050767

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D231/16
ADD.

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 practicable, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2011/061205 A1 (BAYER CROPSCIENCE AG [DE]; PAZENOK SERGII [DE]; LUI NORBERT [DE]; KOST) 26 May 2011 (2011-05-26) cited in the application page 4, line 20 - page 4, line 32 example 1 the whole document -----	1-6
A	WO 2010/130767 A2 (BAYER CROPSCIENCE AG [DE]; BARTELS GUENTER [DE]; BECKER ANGELA [DE]; B) 18 November 2010 (2010-11-18) Step 12, Process P1, page 9 Lines 15-18, page 12 Example IIg-1, page 61 -----	1-6

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

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
11 February 2014	19/02/2014

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	Sarakinos, Georgios

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2014/050767

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011061205 A1	26-05-2011	CN 102666492 A	12-09-2012
		EP 2325173 A1	25-05-2011
		EP 2501682 A1	26-09-2012
		JP 2013511485 A	04-04-2013
		KR 20120084325 A	27-07-2012
		TW 201127817 A	16-08-2011
		US 2011207940 A1	25-08-2011
		US 2013165664 A1	27-06-2013
		WO 2011061205 A1	26-05-2011
WO 2010130767 A2	18-11-2010	AR 076839 A1	13-07-2011
		AU 2010247385 A1	22-12-2011
		CA 2761269 A1	18-11-2010
		CN 102421757 A	18-04-2012
		CO 6460782 A2	15-06-2012
		EA 201171409 A1	30-05-2012
		EP 2430000 A2	21-03-2012
		JP 2012526768 A	01-11-2012
		KR 20120023095 A	12-03-2012
		TW 201043138 A	16-12-2010
		US 2012065164 A1	15-03-2012
		WO 2010130767 A2	18-11-2010