

(19) **DANMARK**

(10) **DK/EP 3060540 T3**



(12) **Oversættelse af
europæisk patentskrift**

Patent- og
Varemærkestyrelsen

-
- (51) Int.Cl.: **C 07 C 49/167 (2006.01)** **C 07 C 45/67 (2006.01)**
- (45) Oversættelsen bekendtgjort den: **2018-10-15**
- (80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2018-06-27**
- (86) Europæisk ansøgning nr.: **14786869.9**
- (86) Europæisk indleveringsdag: **2014-10-20**
- (87) Den europæiske ansøgnings publiceringsdag: **2016-08-31**
- (86) International ansøgning nr.: **EP2014072388**
- (87) Internationalt publikationsnr.: **WO2015059067**
- (30) Prioritet: **2013-10-23 EP 13189817**
- (84) Designerede stater: **AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR**
- (73) Patenthaver: **Bayer CropScience Aktiengesellschaft, Alfred-Nobel-Strasse 50, 40789 Monheim am Rhein, Tyskland**
- (72) Opfinder: **FUNKE, Christian, Herscheid 7, 42799 Leichlingen, Tyskland**
PAZENOK, Sergii, Wipperauer Strasse 57, 42699 Solingen, Tyskland
- (74) Fuldmægtig i Danmark: **RWS Group, Europa House, Chiltern Park, Chiltern Hill, Chalfont St Peter, Bucks SL9 9FG, Storbritannien**
- (54) Benævnelse: **FREMGANGSMÅDE TIL FREMSTILLING AF HALOGENKETONER**
- (56) Fremdragne publikationer:
EP-A1- 0 623 575
DE-A1- 4 313 794

Description

The present invention relates to a novel method for producing haloketones.

5

Haloketones, for example difluoroacetone and trifluoroacetone, are important intermediates in the production of biologically active compounds: WO 2009/000442.

10 Difluoroacetone or trifluoroacetone can be produced from difluoroacetate or trifluoroacetic acid and methylmagnesium bromide for example (Isr. Journal of Chemistry, **1999**, 39, 155). However, the yield for difluoroacetone is just 47% and that for trifluoroacetone is 56%.

15

Di- and trifluoroacetone can also be produced by cleavage of trifluoroacetoacetate in the presence of twenty per cent strength sulphuric acid (Tetrahedron, **1964**, 20, 2163). The disadvantage of this reaction is that it is difficult to find a suitable material of construction which does not corrode and in which the reaction can be carried out. Here, it is not only the sulphuric acid that is the corrosion-causing component but also the liberated fluoride. This combination makes it impossible to use steel enamel, stainless steel and also
20 Hastelloy tanks.
25

EP0623575 (B1) describes the synthesis of ketones by reaction of a carboxylic acid with a ketoester in the presence of a catalytic amount of an onium salt:

30



This method is uneconomical: a carboxylic acid such as CF_3COOH is additionally required. In addition, an ester is formed
35 which causes problems with purifying the product.

The problem addressed by the present invention in view of the prior art described hereinabove is that of providing a method

which does not have the aforementioned disadvantages and consequently provides a route to haloketones in high yields.

The problem described hereinabove was solved by a novel method
5 for producing haloketones of formula (I)

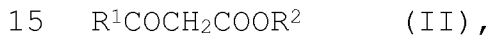


where

10

R^1 is haloalkyl,

characterized in that ketoesters of formula (II)



where

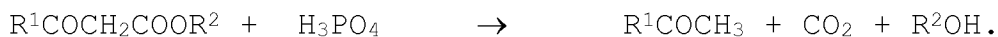
R^2 is alkyl or benzyl and

20

R^1 is as defined above,

are cleaved in the presence of phosphoric acid according to the following scheme:

25



Surprisingly, the haloketones of formula **(I)** are obtained under the conditions of the invention in good yields and with
30 high purity without having strongly corrosive reaction conditions and the method according to the invention consequently overcomes the abovementioned disadvantages of the production methods described in the prior art.

35 Preference is given to a process according to the invention in which the radicals of the compounds of formulas (I) and (II) are defined as follows:

R¹ is selected from CF₃, CF₂H, CF₂Cl;

R² is selected from methyl, ethyl, n-propyl, benzyl.

5 Particular preference is given to a process according to the invention in which the radicals of the compounds of formulas (I) and (II) are defined as follows:

R¹ is CF₂H;

10

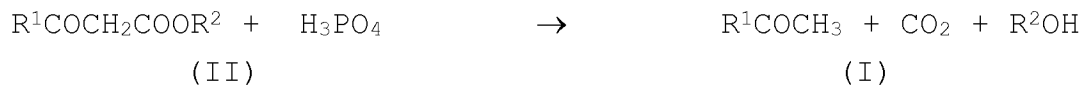
R² is selected from methyl, ethyl.

General definitions

15 **Haloalkyl:** straight-chain or branched alkyl groups having 1 to 6 and preferably 1 to 3 carbon atoms, wherein some or all of the hydrogen atoms in these groups may be replaced by halogen atoms as mentioned above, for example (but not limited to) C₁-C₃-haloalkyl such as chloromethyl, bromomethyl, dichloromethyl,
20 trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chlorofluoromethyl, dichlorofluoromethyl, chlorodifluoromethyl, 1-chloroethyl, 1-bromoethyl, 1-fluoroethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2-chloro-2-fluoroethyl, 2-chloro-2-difluoroethyl,
25 difluoroethyl, 2,2-dichloro-2-fluoroethyl, 2,2,2-trichloroethyl, pentafluoroethyl and 1,1,1-trifluoroprop-2-yl.

Alkyl groups are for the purposes of the present invention linear, branched or cyclic saturated hydrocarbon groups. The
30 definition C₁-C₁₂-alkyl encompasses the widest range defined herein for an alkyl group. Specifically, this definition encompasses the meanings methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and t-butyl, n-pentyl, n-hexyl, 1,3-dimethylbutyl, 3,3-dimethylbutyl, n-heptyl, n-nonyl, n-decyl,
35 n-undecyl or n-dodecyl for example.

Method description

Scheme 1:

5 The ketoester compounds of formula (II) used as starting compounds are known and commercially available. The temperature during the reaction according to the invention is in the range of from 20°C to 200°C, preferably in the range of from 70°C to 130°C.

10

The method according to the invention can optionally be run as a continuous operation.

The quantity of H₃PO₄ is between 5 to 500 g for 1 mol of the
15 compound of formula (I), preferably 20-350 g. Once the product has been isolated, the H₃PO₄ is reused without purification. At least 5 such cycles are possible without a drop in yield. It is preferable to use aqueous H₃PO₄ solution. The concentration of the H₃PO₄ is 20-85%, preferably 85%. It is preferable to use
20 technical-grade material having a content of 70-85%. It is also possible to use polyphosphoric acid. The reaction is optionally carried out in an inert solvent such as chlorobenzene, toluene. Corrosion of glass and metallic materials of construction was not observed for this method.

25

Example 1**Difluoroacetone HCF₂COCH₃**

30 150 ml of H₃PO₄ (85% w/w) were initially charged to a 250 ml multi-necked flask equipped with a distillation bridge and heated to 100°C to 105°C. 132 g of 91% w/w purity ethyl difluoroacetoacetate (0.720 mol) were added over 3 hours via a syringe pump. The distillate of boiling point 40-60°C was
35 continuously removed within 5 hours. The reaction is complete after 5 hours. A total of 75 g of clear colourless liquid were collected.

The composition of the fraction (determined by ^{19}F NMR) is:

70% w/w $\text{HCF}_2\text{COCH}_3$

5

11% w/w $\text{HCF}_2\text{C}(\text{OH})_2\text{CH}_3$ hydrate

14% w/w $\text{HCF}_2\text{C}(\text{OEt})(\text{OH})\text{CH}_3$ monoketal

10 The mixture can be further used without purification. If desired, a second distillation over H_3PO_4 can be carried out for further purification. Hydrate and monoketal are simultaneously cleaved and converted to difluoroacetone.

15 Using 5 g of H_3PO_4 affords after distillation 67 g of difluoroacetone ($\text{HCF}_2\text{COCH}_3$) with a purity of 95% to 96%. The yield is 94% to 95%.

Patentkrav

1. Fremgangsmåde til fremstilling af halogenketoner med formel (I)

5 R^1COCH_3 (I),

hvor

R^1 står for halogenalkyl,

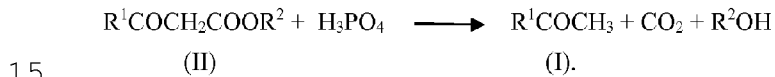
kendetegnet ved, at ketoestere med formel (II)

$R^1COCH_2COOR^2$ (II),

10 hvor

R^2 står for alkyl omfattende lineære, forgrenede eller ringformede mættede carbonhydridgrupper eller benzyl, og R^1 er defineret som ovenfor,

spaltes i nærvær af phosphorsyre ifølge følgende skema:



2. Fremgangsmåde ifølge krav 1, kendetegnet ved, at

R^1 udvælges af CF_3 , CF_2H , CF_2Cl ;

R^2 udvælges af methyl, ethyl, n-propyl, benzyl.

20

3. Fremgangsmåde ifølge krav 1, kendetegnet ved, at

R^1 er CF_2H ;

R^2 udvælges af methyl, ethyl.

25 4. Fremgangsmåde ifølge et af kravene 1 til 3, kendetegnet ved, at den gennemføres ved en temperatur på 70 til 130°C.

5. Fremgangsmåde ifølge et af kravene 1 til 4, kendetegnet ved, at den gennemføres kontinuerligt.