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D E C I S I O N
of 16 November 2004

Case Number: T 0833/02 - 3.3.1

Application Number: 96924795.6

Publication Number: 0842137

IPC: C07C 61/35

Language of the proceedings: EN

Title of invention:

A process for the preparation of cyclopropane carboxylic acids and intermediates therefor

Patentee:

CHEMINOVA AGRO A/S

Opponent:

Syngenta Limited

Headword:

Cis-Cyclopropanes/CHEMINOVA

Relevant legal provisions:

EPC Art. 56

Keyword:

"Main request: inventive step (yes) - non-obvious solution"

Decisions cited:

T 0713/97

Catchword:

-



Case Number: T 0833/02 - 3.3.1

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 16 November 2004

Appellant:
(Proprietor of the patent)

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Decision under appeal:

Decision of the Opposition Division of the
European Patent Office posted 31 May 2002
revoking European patent No. 0842137 pursuant
to Article 102(1) EPC.

Composition of the Board:

Chairman: A. J. Nuss
Members: P. P. Bracke
J. H. Van Moer

Summary of Facts and Submissions

I. The appeal lies from the Opposition Division's decision to revoke European patent No. 0 842 137 since the patent in suit did not meet the requirement of inventive step over the disclosure of documents

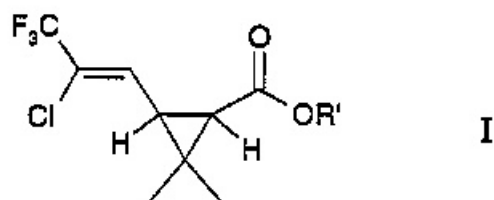
(3) Bull. Chem. Soc. Jpn., 60, 1987, 4385 to 4394,

(5) EP-A-0 187 674 and

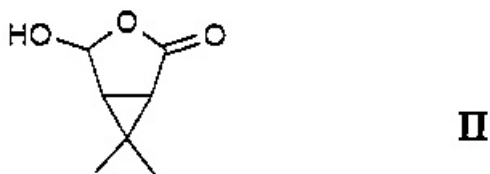
(6) US-A-4 166 063.

The decision was based on the set of claims as granted, which consisted of 7 claims, with the independent claims reading:

"1. A process for the preparation of compounds of the general formula I

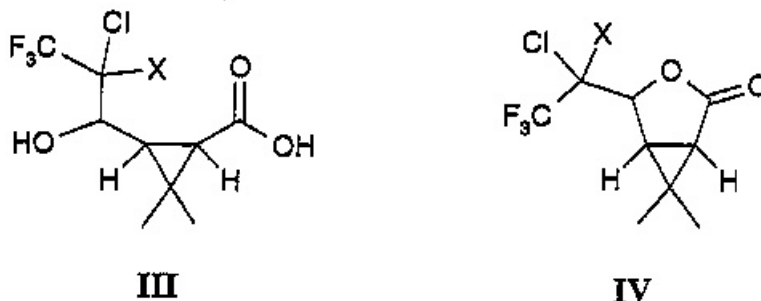


wherein R' represents H, and the two hydrogen atoms on the cyclopropane ring are positioned *cis* to each other, comprising reaction between a compound of the general formula II



and the compound $\text{CF}_3\text{-CClX}_2$, wherein X represents a halogen atom, particularly chlorine or bromine, in an inert medium in the presence of Zn and suitably at

temperatures between 0 and 150°C, preferably between 20 and 100°C, during which reaction the compounds III and IV



occur as intermediates which are not isolated, and when after a period of time analyses show that the starting compound II has been substantially consumed, that the above intermediates III and IV have been formed, and that the end product I has been formed in a minor amount, addition of a dehydrating agent which immediately converts intermediate III into intermediate IV and after a further period of time converts intermediate IV substantially completely into the end product I predominantly as the Z-isomer, in both optically pure and racemic form, care being taken that unreacted metallic zinc is permanently present."

"5. The compound 3-(2,2-dichloro-3,3,3-trifluoro-1-hydroxypropyl)-2,2-dimethyl-(1R,3S)-cyclopropane carboxylic acid (IIIa, X=Cl)"

"6. The compound *cis*-3-(2,2-dichloro-3,3,3-trifluoro-1-hydroxypropyl)-2,2-dimethyl-cyclopropane carboxylic acid (IIIb, X=Cl)."

"7. The compound (1R,5S)-4-(1,1-dichloro-2,2,2-trifluoroethyl)-6,6-dimethyl-3-oxabicyclo[3.1.0]hexan-2-one (IVa, X=Cl)."

- II. The Appellant (Proprietor of the patent) filed with letter of 7 October 2004 sets of claims according to a first to fifth auxiliary request.
- III. The Respondent (Opponent) filed with telefax of 28 May 2004 an additional prior art document, namely document (28) an English translation of *Izv. Akad. Nauk. Ser. Khim. No. 3, 1995, pages 517 and 518.*
- IV. Oral proceedings before the Board took place on 16 November 2004.
- V. The Appellant submitted, that starting from the closest state of the art, namely document (3), the problem underlying the present invention was to provide a process for preparing compounds of formula (I) in a *cis* form. Since document (3) discloses an analogous process to the one claimed for preparing compounds of formula (I) having the *trans* configuration but a fundamentally different process for preparing the *cis*-form of formula (I), the claimed process was inventive.
- VI. The Respondent submitted that document (5) represented the closest state of the art, since the processes described therein had the most features in common with the claimed process. As an epimerisation under the reaction conditions of the claimed process was not to be expected, a skilled person would have expected that the compounds of formula I having the two hydrogen atoms on the cyclopropane ring positioned *cis* to each other could be prepared according to the claimed reaction sequence from 3-formyl-2,2-dimethyl-cyclopropane carboxylic acid having the two hydrogen

atoms on the cyclopropane ring positioned *cis* to each other or its closed form, namely the lactone of formula II. The claimed process was thus obviously derivable from the prior art.

VII. The Appellant requested that the decision under appeal be set aside and that the patent be maintained as granted or, in the alternative, on the basis of any of the first to fifth auxiliary requests filed with letter of 7 October 2004.

The Respondent requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

2. *Main request*

2.1 Since neither all features of the claimed process nor the claimed compounds are disclosed in any of the cited prior art documents, the claims as granted meet the requirement of novelty. As this was not further contested, it is not necessary to give a more detailed reasoning as to whether the requirement of novelty is met.

2.2 Inventive step

In accordance with the "problem-solution approach" applied by the Boards of Appeal to assess inventive step on an objective basis, it is in particular necessary to establish the closest state of the art

forming the starting point, to determine in the light thereof the technical problem which the invention addresses and successfully solves, and to examine the obviousness of the claimed solution to this problem in view of the state of the art.

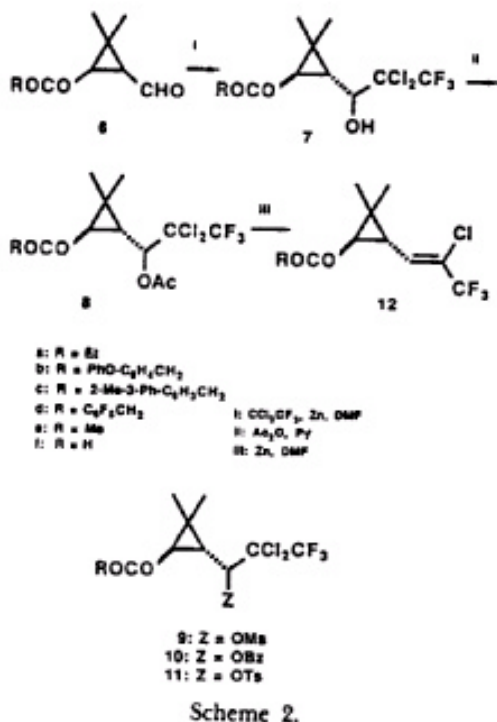
- 2.3 In selecting "the closest state of the art", the first consideration is that it must be directed to **the same purpose** as the claimed invention. Otherwise, it cannot lead the skilled person in an obvious way to the claimed invention (see Case Law of the Boards of Appeal of the European Patent Office, 4th edition 2001, I, D, 3.2). With a prior art not directed to **the same purpose** as starting point, any attempt to establish a logical chain of thought which could lead to the claimed invention, inevitably gets stuck from the outset. In particular, where the background to the invention lies in difficulties encountered in known processes for preparing known compounds, the documents to be considered when determining the closest state of the art are those which describe these compounds and their preparation (T 713/97, point 4.2 of the reasons).

Since the claimed process concerns a process of preparing compounds of formula I wherein the two hydrogen atoms on the cyclopropane ring are positioned *cis* to each other and documents (3) and (28) are the only cited prior art documents disclosing such process for preparing compounds of formula I wherein the two hydrogen atoms on the cyclopropane ring are positioned *cis* to each other, only document (3) or document (28) can be considered as the closest state of the art and, thus, as a suitable starting point for assessing inventive step.

The Board cannot follow the Appellant's opinion, that document (5) represents the closest state of the art due to the fact, that the process described therein has the most features in common with the claimed process. As set out above, what matters is that document (5) is silent about a process for preparing compounds of formula I wherein the two hydrogen atoms on the cyclopropane ring are positioned *cis* to each other and that regardless of how many technical features it may disclose in common with the claimed process.

2.4 Document (3) discloses a stereocontrolled synthesis of 3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethylcyclopropanecarboxylic acid and esters thereof.

2.4.1 Scheme 2 of document (3) reproduced below



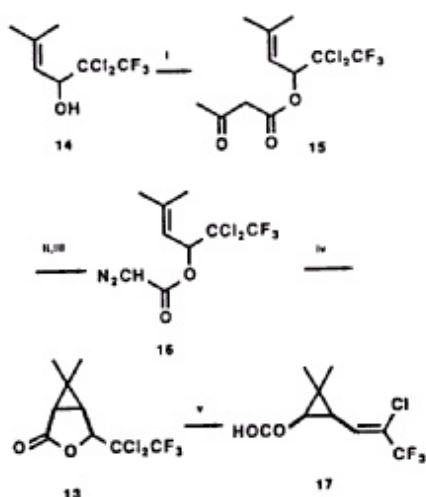
and the corresponding text in the left-hand column on page 4386 describe the reaction sequence, consisting of a reaction of 6 with zinc powder and 1,1,1-trichloro-

2,2,2-trifluoroethan, acetylation of the obtained alcohol **7** and conversion of the acetate **8** with zinc.

2.4.2 In the right-hand column on page 4386 document (3) it is further stated:

"It should be noted that, though *trans/cis* isomeric mixtures (4 to 6:1) of **6** was employed, only *trans*-**6** gave the adduct **7**. The CF_3CCl_2 adducts of the *cis*-**6** apparently underwent lactonization under the reaction conditions to give a bicyclic lactone **13** (<10% yield) which was isolated in some cases. The lactone **13** was not produced from pure *trans*-**6e**. Thus, the correlation of *trans*-**6** to **7** and *cis*-**6** to **13** is disclosed. Since *cis*-**6** is easily epimerized to the *trans*-isomer under the basic conditions, a method is now established for control of the *trans*-configuration on the cyclopropane ring."

2.4.3 Document (3) further discloses in scheme 3



i: ethylene, H_2CO_3
 ii: TaCl_5 , Et_3N
 iii: NaOH
 iv: $\text{Cu}(\text{acac})_2$, heat
 v: Zn , DMF

Scheme 3.

and the corresponding text in the paragraph bridging pages 4386 and 4387 lactone **13** and its conversion with Zn in compound **17**, which is identical with the compound of formula I of present Claim 1. The lactone **13**, which corresponds to a compound of formula IV according to present Claim 1 wherein X = Cl, is, however, prepared following a completely different reaction sequence as the one presently claimed.

2.5 Another stereocontrolled synthesis of 3-(2-chloro-3,3,3,-trifluoro-1-propenyl)-2,2-dimethylcyclopropanecarboxylic acid wherein the two hydrogen atoms on the cyclopropane ring are positioned *cis* to each other is disclosed in document (28). According to that disclosure, an organozinc compound, obtained from CF_3CCl_3 and Zn, is reacted with a mixed anhydride of acetic acid with 3-formyl-2,2-dimethylcyclopropanecarboxylic acid, wherein the two hydrogen atoms on the cyclopropane ring are positioned *cis* to each other, the alcohol obtained is treated with acetic anhydride in pyridine and the obtained acetate is reacted with Zn and subsequently hydrolysed.

2.6 As both documents (3) and (28) are directed to **the same purpose** as the claimed invention. In such case it is the document having the most features in common with the claimed process, which represents the closest state of the art. Since document (3) also describes, as the claimed process, the conversion of the lactone IV into the final compound I, whereas document (28) does not disclose a lactone IV, the process disclosed in document (3) has the most features in common with the claimed process and, thus, represents the closest state of the art.

- 2.7 It has not been contested that, starting from document (3), the problem to be solved consisted in providing a process for preparing compounds of formula I wherein the two hydrogen atoms on the cyclopropane ring are positioned *cis* to each other.
- 2.8 The patent in suit claims to solve this problem by the process defined in Claim 1.
- 2.9 It was also not contested that in the patent in suit, in particular in example 8, it had been made credible that the above-mentioned problem was effectively solved by the process of Claim 1.
- 2.10 Therefore, it remains to be decided whether in the light of the teachings of the cited documents a skilled person seeking to solve the problem as defined in point 2.7 above would have arrived at the process of Claim 1 in an obvious way or not.
- 2.11 From scheme 3 of document (3) it may be concluded that a compound of formula I may be prepared from a lactone **13** and from scheme 2 of document (3) and the paragraph cited in point 2.4.2 it may be concluded that the lactone **13** may not be prepared from *trans*-**6** and only in less than 10% yield from *cis*-**6**. Therefore, from document (3) alone it may not be derived that a compound of formula I wherein the two hydrogen atoms on the cyclopropane ring are positioned *cis* to each other may be prepared from *cis*-**6** or its closed form of formula II as defined in present Claim 1 in a technically and economically attractive manner.

2.12 The Respondent submitted that document (3) was ambiguous as to whether epimerisation could be expected under the conditions described therein. Since from document

(25) Bull. Soc. Chim. Fr., 1964, pages 2693 and 2694,

which is referred to in document (3), and also from document (6) it could be derived that epimerisation would only occur under much more alkaline conditions, a skilled person would not expect epimerisation to occur. Therefore, a skilled person would expect that the compounds of formula I wherein the two hydrogen atoms on the cyclopropane ring are positioned *cis* to each other could be obtained in acceptable yields from 3-formyl-2,2-dimethylcyclopropanecarboxylic acid wherein the two hydrogen atoms on the cyclopropane ring are positioned *cis* to each other, which is in equilibrium with its closed form having the formula II according to present Claim 1. Therefore, the claimed reaction sequence was obviously derivable from document (3).

The passage referred to in document (25) concerns the conversion of the nitrile-group in 2,2-dimethylcyclopropanecyanides bearing in 3-position a butylene group into the corresponding carboxylic acids by potassium hydroxide in hot diethyleneglycol. The mere fact, that it is stated there, that such conditions are epimerisation conditions, however, does not automatically exclude epimerisation under other conditions. Consequently, from the teaching of document (25) it may not be deduced that under the conditions described in document (3) no epimerisation occurs.

Document (6) concerns the reaction of a compound of formula II (according to present Claim 1) with a haloform in the presence of a basic agent, preferably an alcoholate, an alkali metal hydride or an alkali metal hydroxide. In the second full paragraph in column 5 it is stated that, although epimerisation leading to the *trans* compound would have been expected under such alkaline conditions, such epimerisation was not observed. However, since this paragraph continues in stating that the absence of epimerisation is probably due to the greater rate of addition of haloform than the rate of epimerisation, it is at least suggested that the non-observance of epimerisation is rather an exception. Be that as it may, since the disclosure of document (6) is not concerned with a process wherein a compound of formula II is reacted with CF_3CCl_3 in the presence of Zn in dimethylformamide, as disclosed in document (3), it cannot give any indication whether epimerisation could occur under the reaction conditions described in document (3) or not.

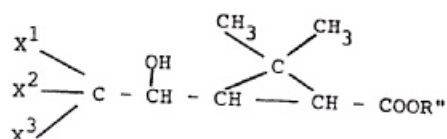
Finally, the Board does not see any ambiguity in the paragraph in document (3) concerning the epimerisation of *cis-6*, since it is clearly stated in the last sentence of the paragraph cited in point 2.4.2 that *cis-6* easily epimerises under the reaction conditions and, thus, a method is established for control of the *trans*-configuration on the cyclopropane ring.

Moreover, the easy epimerisation of 3-substituted-2,2-dimethyl-cyclopropanecarboxylic acid and derivatives thereof is confirmed in the sentence immediately following the sole reaction scheme in document (28), stating that the problem of epimerisation can be

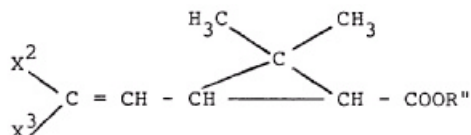
avoided by using a mixed anhydride, since the mild hydrolysis of it makes it possible to avoid epimerisation at the C(1) atom.

2.13 The Respondents argued that the claimed process was obvious due to the teaching of document (5) as such or in combination with the teaching of document (3).

2.13.1 Document (5) discloses compounds of formula



and their preparation by reacting 3-formyl-2,2-dimethyl-cyclopropane carboxylic acid or an ester thereof with a polyhalogenated hydrocarbon $\text{X}^1\text{X}^2\text{X}^3\text{C}$ -halide and a divalent metal, such as zinc, in an aprotic dipolar solvent. Furthermore, document (5) discloses that such compounds may be reduced to the alkenes



e.g. by direct treatment thereof with zinc in acetic acid and that such reduction may be conducted in the same reaction medium in which the carbinol has been prepared without isolating it (see the paragraph bridging pages 1 and 2, page 2, lines 34 to 35, formula (V) and the first and second full paragraph on page 5).

Furthermore, in example 4 a method of preparing ethyl 3-(2,2-dichloro-1-hydroxy-3,3,3-trifluoropropyl)-2,2-dimethyl-cyclopropane carboxylate by reacting Zn powder with CF_3CCl_2 and reacting the thus obtained organozinc compound with ethyl 3-formyl-2,2-dimethyl-cyclopropane

carboxylate (*cis-trans* mixture) is described and in example 25 the conversion of the ethyl 3-(2,2-dichloro-1-hydroxy-3,3,3-trifluoropropyl)-2,2-dimethyl-cyclopropane carboxylate into ethyl 3-(2-chloro-3,3,3-trifluoropropenyl)-2,2-dimethyl-cyclopropane carboxylate by the successive steps of preparing the acetate and treating it with Zn powder is described.

Finally, in example 27 a one-pot process of preparing 2-chloro-3,3,3-trifluoro-1-phenyl-1-propene is described by reacting benzaldehyde with CF_3CCl_3 in the presence of Zn, subsequently treating the obtained product with acetic anhydride and then treating the reaction mixture with Zn.

2.13.2 Since document (5) is not concerned with a stereocontrolled synthesis of 3-(2-chloro-3,3,3,-trifluoro-1-propenyl)-2,2-dimethylcyclopropanecarboxylic acid, let alone with the synthesis of such compounds wherein the two hydrogen atoms on the cyclopropane ring are positioned *cis* to each other, the claimed process cannot be obviously derivable from the disclosure of document (5) alone (see point 2.3 above).

2.13.3 Therefore, in assessing inventive step the question remains whether, starting from the disclosure of document (3), document (5) could give any indication to a skilled person towards the proposed solution for solving the problem cited in point 2.7 above.

Since all reaction features of Claim 1 were disclosed in document (5), the Respondent was of the opinion that it provided a sufficient hint, so that the claimed process was rendered obvious.

However, as the general teaching of document (5) is completely silent about a process for preparing 3-(2-chloro-3,3,3,-trifluoro-1-propenyl)-2,2-dimethylcyclopropanecarboxylic acid **wherein the two hydrogen atoms on the cyclopropane ring are positioned *cis* to each other**, such general teaching cannot give any indication for the particular problem underlying the present invention.

It is true that in example 4 it is specified that a *cis-trans* mixture of ethyl 3-formyl-2,2-dimethyl - cyclopropanecarboxylate is used as starting material. However, in example 4 the ethyl ester and not the carboxylic acid, which may be in equilibrium with the lactone of formula II according to Claim 1, is used as starting material and it is only stated there that the carbinol obtained is a *cis-trans* mixture 45:55. Thus, in the absence of any indication about the *cis-trans* isomer-ratio of the starting compound, example 4 does not provide any information about the stereoselectivity of the reaction. Moreover, since in example 25 for the conversion of the carbinol obtained in example 4 in the 3-(2-chloro-3,3,3,-trifluoro-1-propenyl)-2,2-dimethylcyclopropanecarboxylic acid no further information about the stereochemical forms is given, also example 4 in combination with example 25 cannot give any hint to the claimed process.

Finally, since example 27 describes the reaction of CF_3CCl_3 with benzaldehyde, where epimerisation may not occur, also example 27 does not point to the claimed process.

2.14 Consequently, the claimed process is not rendered obvious for the reason that it could not be deduced from the combined teaching of documents (3) and (5) that the compounds of formula I could be obtained from a lactone of formula II.

2.15 Since no further pointer to the claimed solution could be found in any of the remaining cited documents, the process of Claim 1, and by the same token, that of dependent claims 2 to 4 meets the requirement of inventive step.

The compounds claims 5, 6 and 7, concerning intermediates formed during the claimed process, derive their patentability from the same inventive concept as Claim 1.

3. *Auxiliary requests*

In the light of the above findings, there is no need to consider the auxiliary requests.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The patent is maintained as granted.

The Registrar:

The Chairman

N. Maslin

A. Nuss