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DECISION
of 6 July 1994

Case Number:	T 0091/92 - 3.3.1
Application Number:	83112986.1
Publication Number:	0113107
IPC:	C07C 29/42
Language of the proceedings:	EN

Title of invention:
Process for preparing alcohols

Patentee:
Sumitomo Chemical Company, Limited

Opponent:
G. D. Searle & Co.

Headword:
Magnesium activator/Sumitono

Relevant legal norms:
EPC Art. 56

Keyword:
"Inventive step (yes)"
"Search for solving the problem - a matter of mere chance"

Decisions cited:
-

Catchword:
-

Case Number: T 0091/92 - 3.3.1

DECISION
of the Technical Board of Appeal 3.3.1
of 6 July 1994

Appellant:
(Opponent)

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Representative:

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Decision under appeal:

Decision of the Opposition Division of the European Patent Office delivered orally on 22 October 1991, with written reasons posted on 2 December 1991, rejecting the opposition filed against European patent No. 0 113 107 pursuant to Article 102(2) EPC.

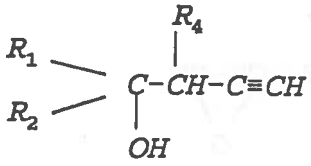
Composition of the Board:

Chairman: A. Jahn
Members: P. P. Bracke
R. E. Teschemacher

Summary of Facts and Submissions

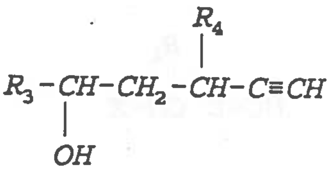
I. European patent No. 0 113 107 in respect of European patent application No. 83112986.1 was granted on 7 June 1989 (cf. Bulletin 89/23) with 5 claims. The only independent claim reads as follows:

"A process for preparing an alcohol of the formula



(I)

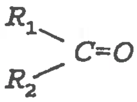
or



$$R_3-\underset{\displaystyle OH}{\underset{|}{CH}}-CH_2-\overset{\displaystyle R_4}{\overset{|}{CH}}-C\equiv CH$$

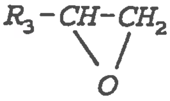
(I')

wherein R1 and R2 are, same or different, each a hydrogen atom, a straight, branched or cyclic alkyl, alkenyl or alkynyl group having not more than 14 carbon atoms, a phenyl group, a naphthyl group, a benzyl group, a furyl group or a thienyl group, provided that when either one of R1 and R2 represents a hydrogen atom, the other is not a hydrogen atom, R3 is a hydrogen atom, a straight or branched alkyl group having not more than 6 carbon atoms or a phenyl group and R4 is a hydrogen atom or a methyl group by reacting a carbonyl compound of the formula:



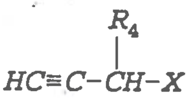
(II)

wherein R1 and R2 are each as defined above, or an oxirane of the formula:



(III)

wherein R3 is as defined above, magnesium and a propargyl halide of the formula:



$HC\equiv C-\overset{R_4}{\overset{|}{C}}H-X$

(IV

wherein X is a halogen atom and R4 is as defined above, followed by hydrolysis, characterized in that the carbonyl compound (II) or the oxirane compound (III) and the propargyl halide (IV) are reacted simultaneously onto magnesium in an inert solvent in the presence of zinc or its halide."

II. A notice of opposition was filed on 3 March 1990 by G. D. Searle & Co., requesting the revocation of the patent on the ground of lack of inventive step. The opposition was supported by several documents including:

D1: US-A-4 087 468,
D2: US-A-2 813 886,
D3: US-A-4 085 272,
D4: J. Med. Chem. **20**, 1152-1159 (1977),
D6: J. Am. Chem. Soc, **54**,
1943-1947 (1932) and
D9: Synthesis, 18-30 (1977)

which are relevant for the present decision.

III. By a decision delivered orally on 22 October 1991, with written reasons posted on 2 December 1991, the Opposition Division rejected the opposition.

The Opposition Division held that it could not have been foreseen from the prior art that the replacement of mercuric chloride by zinc or a zinc halide in the process of reacting a propargyl halide, magnesium and mercuric chloride with a carbonyl-compound or an oxirane would result in the formation of alcohols with improved yields, as shown by a comparative example, filed on 7 October 1991, repeating the example described in the last paragraph in the left-hand column of page 1156 of D4, but replacing mercury chloride by zinc bromide, further referred to herein as "the comparative test".

IV. An appeal was lodged against this decision on 29 January 1992 with payment of the prescribed fee. In the statement of grounds of appeal filed on 2 April 1992 and during the oral proceedings on 6 July 1994 the Appellant (Opponent) argued that the skilled man, being well aware of the unpredictability of the yield of products in chemical reactions, was inevitably lead to replace mercuric halide as magnesium activator in the reactions known from D3, D4 and D9 by zinc or its halide, since it was known from D1, D6,

D11: Rec. Trav. Chem. **47**, 19-21 (1928) and
D12: "Grignard Reactions of Non-metallic Substances,
Chapter II, pages 5, 8-11 (1954)

that zinc or its halide and mercuric halides are both useful activators for magnesium.

Additionally, it was contested that the claimed process results into an improved yield, because table 3 of D9 already described the preparation of alcynols falling within the terms of Claim 1 of the disputed patent by reaction of a propargyl bromide with activated magnesium and 2-pentanone in yields of 70 and 85%.

Finally, an affidavit signed by James Richard Behling was filed. Therein the validity of the yield data in the comparative test was contested, because it was concluded from a pressure-temperature nomograph that the obtained 1-octyn-4-ol was not pure. It was also submitted that exhibits A, D and E demonstrated that, by using mercuric chloride in the reaction described in example 1 of D4, yields superior or similar to those mentioned in the contested patent were obtained.

V. The Respondent (Patentee) submitted that it was nowhere suggested that the replacement of a mercuric halide by zinc or its halide as magnesium activator in the reaction of a propargylhalide with a carbonyl compound would result in improved yields. In particular, it was argued that D1 only taught that halides of zinc and other metals influence the ratio of conjugated to allenic dienols in a reaction of 1- or 2-halo-1,3-hydrocarbyl diene; from D6 it may only be concluded that zinc is a useful catalyst in the preparation of the Grignard reagent of allyl bromide, not in the case of a propargyl halide; and D11 and D12 only mention the interchangeability of zinc and mercury activators.

It was also argued that the skilled man faced with the problem of substituting the environmentally dangerous mercury, was not forced to use zinc, because in the reaction of an halide with a carbonyl compound and magnesium the metal may be activated in many different ways and it was not foreshadowed that by using zinc or its halide instead of mercury halide increased yields would be obtained.

It was also argued that the yields described in table 3 of D9 should be disregarded, because it was not clear from the general procedure described on page 25 of D9 whether iodine or mercuric chloride was used as magnesium activator.

Additionally, the Respondent contested the yield-data mentioned in the affidavit, because those data are obtained by the calculation of gas chromatographic data, which are not comparable with the yields obtained after distillation of a reaction mixture.

VI. The Appellant requested that the decision under appeal be set aside and the patent be revoked.

The Respondent requested that the appeal be dismissed.

VII. At the conclusion of the oral proceedings, the Board's decision to dismiss the appeal was pronounced.

Reasons for the Decision

1. The appeal is admissible.

2. The only issue before the Board is whether Claim 1 meets the requirement of inventive step.

3. *Closest state of the art*

The disputed patent relates to a process for preparing alcynols by reacting carbonyl compounds or oxiranes with propargyl halides and magnesium in a one-step reaction. In the description of the disputed patent it is acknowledged that this reaction was known (page 2, lines 39 to 42 of the printed patent specification).

With respect to this process, the Board considers D3 as the closest state of the art. This discloses the preparation of alcynols from carbonyl compounds with a propargyl halide simultaneously on magnesium, wherein the magnesium is activated by mercuric chloride (cf. Flowsheet D in column 17 in text with examples 93 to 97).

Example 93 of D3 gives a relatively low yield of 1-octyn-4-ol (36 g corresponds with 28.5%) but states that additional product can be obtained by redistillation of the higher-boiling and lower-boiling distillates. Having regard to the last paragraph in the left-hand column on page 1156 of D4, according to which 1-octyn-4-ol was obtained by the reaction of valeraldehyde and propargylbromide on magnesium activated with mercuric chloride in 60% yield, the Board considers this figure representative for the reaction under consideration. Moreover, in the absence of evidence to the contrary, this yield is regarded by the

the Board as a typical value which can be roughly generalised for the entire known process.

4. *Problem and solution*

From the description of the contested patent it can be inferred that the object of the invention was to replace the ecologically harmful mercuric halide as activator in the known reaction of carbonyl compounds and propargyl halides with magnesium and, at the same time, to obtain the reaction products with excellent yield and high purity (see page 2, lines 43 to 45, and page 4, lines 1 to 3, of the contested patent).

In view of the yields given in the experimental part of the patent in suit (81 to 90%) and the yield data of the comparative test (89%), the Board considers the technical problem underlying the disputed patent vis-à-vis the closest prior art to lie in proposing a process of the same type which is environmentally less harmful and provides improved yields. The solution of this problem consists of replacing mercuric halide by zinc or its halide. The Board is satisfied that this problem is effectively solved.

The Board cannot accept the Appellant's argument that table 3 of D9, giving a yield of 70 or 85% for the preparation of two alcynols falling within the terms of Claim 1 by reactions of 2-pentanone with propargylbromides and magnesium activated with mercuric chloride, is evidence that the claimed process is not associated with improved yields, because it is not clear from D9 whether the magnesium was activated with iodine or mercuric chloride (cf. page 25 under "General Procedure").

However, even assuming in the Appellant's favour that for the above yields listed in this table the magnesium would have been activated with mercuric chloride, this does not permit the conclusion that the claimed process does not result in increased yields, because the Appellant, on whom the burden of proof rests, failed to provide experiments supporting this allegation.

5. The Board is also unable to accept that the data in the exhibits A, D and E annexed to the affidavit signed by James Richard Behling are sufficient proof that 1-octyn-4-ol can be obtained according to the process described in D4, page 1156, last paragraph of the left-hand column, by using magnesium activated with mercuric chloride in yields superior or similar to the corresponding process using zinc bromide as magnesium activator, as described in the Respondent's comparative test.

Exhibits A and D show by way of gas chromatographic analysis data that the 1-octyn-4-ol was contained in the organic solution, obtained at the end of the reaction, in an amount corresponding to a yield of 96 and 72.6% respectively based on starting valeraldehyde.

In the Board's judgement the yield obtained in this reaction must not be calculated by the analytical determination of the content of the desired product in the reaction mixture but by the effectively isolated amount. Thus the yields found by gas chromatographic analysis, which inexplicably vary at 23%, are disregarded by the Board.

However, the yields determined in exhibits A, D and E by isolating 1-octyn-4-ol by way of distillation are 67, 54.6 and 71% respectively (average 64%) and thus confirm the result achieved in D4 and demonstrate that the process of the disputed patent (yield of 1-octyn-4-ol 89%) results in yields superior to those of the closest prior art.

6. The Appellant tried to undermine the credibility of the results of the comparative test by a series of arguments. He submitted, that it was doubtful whether the fraction obtained was really 1-octyn-4-ol. In this context the Appellant criticised the fact that the Respondent's reaction product was not defined by e.g. gas chromatographic data or NMR-data. This objection fails because it is unusual in patent literature to further characterise a known compound like 1-octyn-4-ol by chromatographic or spectroscopic data. It can be expected that a skilled worker who has good reason to have obtained a known chemical entity will check its identity without therefore publishing the determined physical parameters.

The Appellant further relied on the argument that the 1-octyn-4-ol obtained according to the example in D4 had a boiling range of 33-34°C at 0.2 mm Hg, contrary to the boiling range of the 1-octyn-4-ol obtained according to the comparative test, which is 62-64°C at 10 mm Hg. He concluded from this that by using a pressure-temperature nomograph it is apparent that the 1-octyn-4-ol obtained according to the comparative test was not pure and, consequently, that the effective yield of the comparative example is lower than indicated.

The Board cannot accept this as sufficient proof that the 1-octyn-4-ol obtained according to the comparative example is not sufficiently pure, because, as the Appellant admitted during the oral proceedings, the pressure-temperature nomograph is a very rough method for predicting boiling points at different pressures and there is no reliable relation between the data of such nomograph and the purity of the concerned compound. Additionally, the pressure-temperature nomograph used was not specifically constructed for 1-octyn-4-ol and, consequently, the data obtained by such general nomograph are to be used with extreme care.

Moreover, it is not permissible to cast doubts on established facts without substantiating these doubts by way of verifiable facts. In the present case it was up to the Appellant (Opponent) to show that the distillation fraction obtained at 62-64°C at 10 mm Hg was not pure 1-octyn-4-ol but contained side products in amounts reducing the yield of 1-octyn-4-ol considerably. In the absence of such evidence and in view of the considerable difference in yields between the reaction described in the comparative example (89%) and the reactions described in exhibits A, D and E (64% on average), the Board rejects the Appellant's "impurity" argument.

7. The Appellant also criticised the fact that the amount of zinc bromide used in the comparative test was 13.5 g whereas the amount of mercuric chloride used in the example of D4 was only 200 mg and concluded that the comparison was not correctly made. In the Board's judgement this objection is unjustified. On the one hand, the amount of zinc bromide used in the comparative example corresponds to the amounts of zinc activator used in the examples of the patent in suit and is clearly representative for the performance of the disputed process. On the other hand, it is legitimate for the purpose of demonstrating improved yields to compare the two processes in their representative embodiments. The comparative test meets these requirements and, hence, is conclusive.

8. *Assessment of inventive step*

As set out above, D3, which represents the closest prior art, discloses all the features of the claimed process, save the use of zinc or a zinc halide as activator of the magnesium. Thus, the question to be answered is whether the skilled person faced with the above technical problem would have deduced from the cited prior art the solution suggested by the disputed patent.

The Appellant has admitted during the oral proceedings, that an expert forecast of yields of a desired product in chemical preparation methods, also the ones looked at in the present case, is generally impossible. Thus the question whether the solution to the existing problem, which is essentially based on improved yields, was obvious is already answered in the negative.

However, the Appellant submitted that a skilled man would inevitably have been lead by D1 to replace the mercuric chloride as magnesium activator in the reactions known from D3 and D4 by zinc or its halide, because from the four magnesium activators disclosed there cadmium halides and, of course, mercuric halides would be disregarded due to their serious ecological drawbacks, the elimination of which was part of the present problem. From the remaining alternatives, zinc and indium halides, the skilled person's choice would clearly have been zinc halides for economical reasons (cost, access). In the Board's judgement, however, this stance is the result of an oversimplification.

When considering the known methods of activating magnesium in a Grignard reaction, the prior art suggested further metal halides, like cupric or gold chloride (cf. D12, page 11, last paragraph), and numerous other activators, for example, preformed

Grignard reagent, iodine, bromine, alkyl halides, hydrogen halides, ethyl orthosilicate, magnesium alloys (see, for example, D12, page 8, third paragraph up to page 11, last paragraph, and D11 page 19). Due to the host of possibilities, without any reasonable chance of success in solving the posed problem, and due to the fact that the search for a suitable activator was a matter of mere chance, the special choice of zinc and zinc halides is an indication of inventive step.

Moreover, D1, D2, D6, D11 and D12 are not concerned with the **simultaneous** reaction of an halide and a carbonyl compound on magnesium and none of those documents teaches that zinc or zinc halide would be a suitable activator for the reaction of a **propargyl halide** with a carbonyl compound and magnesium.

D1 teaches that by changing the ratio metal halide : halo-diene in the reaction of 1- or 2-halo-1,3-dienes with activated Mg in the presence of a saturated aliphatic halide the relative amounts of conjugated versus allenic dienols can be influenced, but is silent about the Grignard reaction of a propargyl halide; D2 teaches a method of increasing the yield of arylhalosilanes in the reaction between an arylmagnesium halide and a silicon halide, which process is unrelated to the one under consideration; D6 discloses that the addition of zinc to the reaction mixture increases the yield of the Grignard reagent in the case of allyl bromide and also that such effect was not observed upon other halides (alkyl, cycloalkyl and benzyl halides) and that mercuric chloride depending upon the halide increases or decreases the yield of the Grignard reagent. This does not allow any conclusion how propargyl halides would behave. D11 and D12 are concerned with activation of magnesium for the preparation of Grignard reagents in general, without mentioning propargyl halides.

The Appellant did not provide any evidence for his assertion that, due to the structural similarity of allyl bromide and propargyl bromides, a similar reactivity in Grignard reactions could be expected. In this respect also D6 is to be considered, which teaches that zinc as activator increases the yield of the Grignard reagent only in the reaction with allyl bromide without having any effect on the other halides listed in Table III (i.e. alkyl-, cycloalkyl- and benzyl halides) but mercuric chloride in some cases markedly increased the yield of Grignard reagent. This teaching cannot be regarded as an invitation to use zinc or its halide, let alone for the purpose of the preparation of alcynols, it rather points away from the invention.

9. Therefore, in the Board's judgement, the proposed solution to the technical problem is inventive. Thus, Claim 1 and Claims 2 to 5, which relate to preferred embodiments of the process according to Claim 1, are allowable.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

E. Görgmaier A. Jahn

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