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Datasheet for the decision of 7 September 2010

Case Number: T 1624/08 - 3.3.10

Application Number: 01304872.3

Publication Number: 1160236

IPC: C07C 51/56

Language of the proceedings: EN

Title of invention:
Production of mixed acid anhydride and amine compound

Patentee:
Sumitomo Chemical Company, Limited

Opponent:
Dr Klusmann Peter

Headword:
-

Relevant legal provisions:
EPC Art. 56

Relevant legal provisions (EPC 1973):
-

Keyword:
"Inventive step (no): improvement (yes) - solution already in prior art"

Decisions cited:
T 1711/06

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1624/08 **-** 3.3.10

D E C I S I O N
of the Technical Board of Appeal 3.3.10
of 7 September 2010

Appellant: (Patent Proprietor)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 9 June 2008 revoking European patent No. 1160236 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairman: R. Freimuth
Members: P. Gryczka
J.-P. Seitz

Summary of Facts and Submissions

I. An opposition was filed in which entire revocation of European patent 1 160 236 was requested on the ground that the claimed subject-matter lacked novelty and inventive step (Article 100(a) EPC) in view, *inter alia,* of documents

(1) JP-A 06-321946 in the form of its translation into English

(2) US-A 3 264 281,

(3) US-A 3 640 991 and

(5) "A reinvestigation of the mixed carbonic anhydride method of peptide synthesis", G.W. Anderson et al., Journal of the American Chemical Society (1967), pages 5012 to 5017.

Claim 1 of the granted patent (present main request) reads as follows:

"1. A method for producing a mixed acid anhydride of formula (1):

$$R^1C(O)OY(O)_n(R^2)_p$$

wherein R^1 denotes
a hydrogen atom,
an optionally substituted saturated or unsaturated hydrocarbyl group, or
an optionally substituted hetero ring;
R^2 denotes

an optionally substituted alkyl group,
an optionally substituted aryl group,
an optionally substituted chain or cyclic alkoxy group,
or an optionally substituted aryloxy group;
Y denotes
a carbon atom, a phosphorus atom, or a sulfur atom; n and p are an integer of 1 or 2; and
when Y is a carbon atom, n=1 and p=1,
when Y is a phosphorus atom, n=1 and p=2, and
when Y is sulfur atom, n=2 and p=1 and R^2 denotes an optionally substituted alkyl or aryl group;
which method comprises adding a carboxylic acid of formula (2):

$$R^1COOH$$

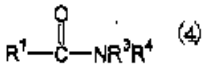
wherein R^1 is as defined above, and N-methylmorpholine to a solution of a carboxylic acid activating agent of formula (3):

$$(R^2)_pY(O)_nX$$

wherein R^2, Y, n and p are as defined above, and
X denotes
a fluorine atom, a chlorine atom, a bromine atom, an iodine atom, a cyano group or a group of formula: $(R^2)_pY(O)_nO$-, wherein R^2, Y, n and p are as defined above."

Claim 2 as granted (main request) reads as follows:

"2. A method according to claim 1, which further comprises producing an amide compound of formula (4):



wherein R^1 denotes
a hydrogen atom,
an optionally substituted saturated or unsaturated hydrocarbyl group, or an optionally substituted hetero ring;
R^3 and R^4 independently denote
a hydrogen atom,
an optionally substituted saturated or unsaturated hydrocarbyl group,
an optionally substituted hetero ring, or
a protective group for an amino group, or
R^3 represents a group of formula: $-OR^{30}$, or $-NR^{30}R^{31}$, wherein R^{30} represents an optionally substituted alkyl group, or an optionally substituted aryl group and R^{31} represents a hydrogen atom or an optionally substituted aryl group, and
R^3 and R^4 may together form a ring;
which method comprises
by reacting a mixed acid anhydride of formula (1), obtained by a method as claimed in claim 1, with an amine of formula (5)

$$NHR^3R^4 \quad (5)$$

wherein R^3 and R^4 are as defined above."

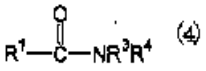
II. In an decision issued in writing on 9 June 2008, the Opposition Division revoked the patent. The Opposition Division came to the conclusion that the subject-matter of the then pending main request and first auxiliary request was not novel over document (1) and that the process according to the claims of the second and third

auxiliary requests then pending did not involve an inventive step, inter alia, in view of the teaching of documents (2) and (3).

III. The Proprietor (Appellant) lodged an appeal against the above decision. With a letter dated 8 October 2008 the Appellant filed four amended sets of claims as auxiliary requests 1 to 4. With a letter dated 6 August 2010 he filed a further set of claims as auxiliary request 5. At the oral proceedings held before the Board on 7 September 2010 the Appellant withdrew the auxiliary request 4.

Claim 1 of the auxiliary request 1 reads as follows:

"1. A method for producing an amide compound of formula (4):



wherein R^1 denotes
a hydrogen atom,
an optionally substituted saturated or unsaturated hydrocarbyl group, or an optionally substituted hetero ring;
R^3 and R^4 independently denote
a hydrogen atom,
an optionally substituted saturated or unsaturated hydrocarbyl group,
an optionally substituted hetero ring, or
a protective group for an amino group, or
R^3 represents a group of formula: $-OR^{30}$, or $-NR^{30}R^{31}$,
wherein R^{30} represents an optionally substituted alkyl group, or an optionally substituted aryl group and R^{31}

represents a hydrogen atom or an optionally substituted aryl group, and
R^3 and R^4 may together form a ring;
which method comprises
(A) producing a mixed acid anhydride of formula (1):

$$R^1C(O)OY(O)_n(R^2)_p \quad (1)$$

wherein R^1 is as defined above,
R^2 denotes
an optionally substituted alkyl group,
an optionally substituted aryl group,
an optionally substituted chain or cyclic alkoxy group,
or an optionally substituted aryloxy group;
Y denotes
a carbon atom, a phosphorus atom, or a sulfur atom; n and p are an integer of 1 or 2; and
when Y is a carbon atom, n=1 and p=1,
when Y is a phosphorus atom, n=1 and p=2, and
when Y is sulfur atom, n=2 and p=1 and R^2 denotes an optionally substituted alkyl or aryl group;
wherein a carboxylic acid of formula (2):

$$R^1COOH \quad (2)$$

wherein R^1 is as defined above, and N-methylmorpholine are added to a solution of a carboxylic acid activating agent of formula (3):

$$(R^2)_pY(O)_nX \quad (3)$$

wherein R^2, Y, n and p are as defined above, and
X denotes

a fluorine atom, a chlorine atom, a bromine atom, an iodine atom, a cyano group or a group of formula: $(R^2)_pY(O)_nO$-, wherein R^2, Y, n and p are as defined above,

and

(B) reacting the mixed anhydride of formula (1) thus obtained with an amine of formula (5)

$$NHR^3R^4 \quad (5)$$

wherein R^3 and R^4 are as defined above."

Claim 1 of the auxiliary request 2 differs from claim 1 of the main request (patent as granted) by the addition of the word "simultaneously" before the expression "a carboxylic acid of formula (2)".

Claim 2 of the auxiliary request 2 reads as claim 2 of the main request.

Claim 1 of the auxiliary request 3 differs from claim 1 of the auxiliary request 1 by the addition of the word "simultaneously" before the expression "to a solution of a carboxylic acid activating agent of formula (3)".

Claim 1 of the auxiliary request 5 differs from claim 1 of the auxiliary request 1 by a restricted definition of the amide compound of formula (4) specifying that in formula (4)
"R1 denotes a group

wherein R^5 and R^6 independently represent a hydrogen atom or a saturated or unsaturated hydrocarbyl group or a hetero ring, both of which may be substituted with
(a) a hydroxy group or a halogen atom, or
(b) at least one group selected from
a carbamoyl group, a methylmercapto group, an alkyl(C1-C3)dithio group, of which alkyl is substituted with a protected amino and carboxyl groups, and
an amino, mercapto, guanidyl, carboxyl, hydroxy or imidazolyl group,
R^{11} is a hydrogen atom or a Boc amino-protecting group,
R^{12} represents a Boc amino-protecting group or a group of formula: $R^{13}CO$-, wherein R^{13} represents a saturated or unsaturated hydrocarbyl group or a hetero ring, which may be substituted with
(c) a hydroxy group or a halogen atom, or
(e) a group of formula: $R^{14}R^{15}N$- and optionally further with at least one group selected from
a carbamoyl group, a methylmercapto group, an alkyl(C1-C3)dithio group, of which alkyl is substituted with a protected amino and carboxyl groups, and
an amino, mercapto, guanidyl, carboxyl, hydroxy, or imidazolyl group,
wherein R^{14} is an amino-protecting group, and R^{15} represents a hydrogen atom or an amino-protecting group, and
R^{11} and R^{12}, and R^{14} and R^{15} may independently form an alkyleneimine group, a 4-pyrimidinone-3-yl group,
provided that said amino, mercapto, guanidyl, carboxyl, hydroxy and imidazolyl groups which may be present in R^{11}, R^{12}, R^5 and R^6 or substituent groups contained therein are in a protected form;
R^3 and R^4 independently denote

a hydrogen atom,
an optionally substituted saturated or unsaturated hydrocarbyl group,
an optionally substituted hetero ring, or
a protective group for an amino group, or
R^3 represents a group of formula: $-OR^{30}$, or $-NR^{30}R^{31}$, wherein R^{30} represents an optionally substituted alkyl group, or an optionally substituted aryl group and R^{31} represents a hydrogen atom or an optionally substituted aryl group, and
R^3 and R^4 may together form a ring".

IV. According to the Appellant, the claimed subject-matter was novel. For the assessment of inventive step document (3) represented the closest prior art and the problem underlying the present invention was to improve the selectivity of the process for the desired product, improving thereby the yield of the reaction. The solution proposed by the patent in suit was characterized by the specific order of addition of the reactants, i.e. adding the carboxylic acid and the N-methylmorpholine to a solution of a carboxylic acid activating agent. The results observed in example 12 and comparative example 2 of the patent specification demonstrated that the defined problem was effectively solved by the claimed process. The process described in the closest prior art document (3) required a base having a specific electronegativity. Such bases were not disclosed in document (2) which therefore could not suggest the claimed solution. Document (5) which taught that N-methylmorpholine was the preferred base for preparing mixed anhydrides, disclosed nevertheless only triethylamine as base when the order of addition of the reactants was the same as defined in the patent in suit.

If it would have been obvious for the skilled person to use N-methylmorpholine with the order of addition of the reactants required by the patent-in suit this would have been disclosed in document (5) or at least later in document (3) which was from the same research group. Therefore the solution proposed was not obvious even in view of the teaching of document (2). Thus, the claimed subject-matter involved an inventive step.

V. According to the Respondent (Opponent), the process according to claim 1 of the main request and the auxiliary request 1 was not novel in view of document (1). The amendments carried out in claim 1 of the auxiliary request 5 extended the claimed subject matter beyond the content of the application as filed since there was no basis for R^{11} and R^{12} being both a Boc protecting group. For the assessment of inventive step document (3) represented the closest prior art. The problem underlying the present invention of improving the selectivity of the process for the desired product, improving thereby the yield of the reaction was however not solved. In fact, the results observed in example 12 and comparative example 2 of the patent specification could not be compared since the acid treatment and the analysis of the product were different in both examples. Therefore, the Appellant did not show properly that an improvement was achieved with the claimed process. In any case even if an improvement was acknowledged, the solution proposed by the patent in suit in order to achieve such improvement was obvious for a skilled person, since it was known from document (2) that the claimed order of addition of the reactants, i.e. adding the carboxylic acid and the N-methylmorpholine to a solution of a carboxylic acid activating agent was

beneficial in terms of yield of the reaction. Therefore, the claimed process did not involve an inventive step.

VI. The Appellant requested that the decision under appeal be set aside and that the patent be maintained as granted or, subsidiarily, on the basis of one of the auxiliary requests 1 to 3 filed with letter dated 8 October 2008, or further subsidiarily on the basis of auxiliary request 5 filed with letter dated 6 August 2010.

VII. The Respondent requested that the appeal be dismissed.

VIII. At the end of the oral proceedings the decision of the Board was announced.

Reasons for the Decision

1. The appeal is admissible.

Auxiliary request 5

2. *Amendments*

Claim 1 is based on the combination of claims 1, 2 and 7 of the application as filed. R^{11} and R^{12} are described in claim 7 as filed as representing , *inter alia*, an amino-protecting group. The definition of the amino protecting groups is disclosed on page 13, lines 19 to 27, whereof it can be taken directly and unambiguously that the preferred amino-protecting group is Boc (page 13, line 27). Therefore the application as filed provides support for R^{11} and R^{12} being, inter alia,

a Boc amino-protecting group. Hence, the amendments of claim 1 fulfil the requirements of Article 123(2) EPC. It is not in dispute that the amended claim 1 restricts the protection conferred by the patent as granted (Article 123 (3) EPC.

3. *Novelty*

Novelty of the subject matter of claim 1 of the auxiliary request 5 is not in dispute and the Board on its side sees no reason to raise such an objection on its own.

4. *Inventive step*

Since the method according to claim 1 of the auxiliary request 5 is encompassed by claim 2 of the main request and of auxiliary request 1 it is appropriate in the present case that first the subject-matter of claim 1 of said auxiliary request 5 be examined as to its inventive ingenuity.

4.1 The patent in suit is directed to a method for producing an amide involving the preparation of an intermediate mixed anhydride. It is not disputed by the parties that document (3) also relates to such a method, involving the same starting products than the process according to claim 1 in dispute and that document (3) discloses already the combination of Boc-amino protecting groups (named tertiarybutyloxycarbonyl) with the use of N-methylmorpholine as a base (claims 1, 2, and 4). Although document (3) describes a specific order of addition of the reactants, namely the addition

of the carboxylic acid activating agent, i.e. isobutyl chloroformate, to N-methylmorpholine and an acid, i.e. carbobenzoxyglycyl-L-phenylalanine (example 1), it is further accepted by both parties that document (3), in its general teaching, does not define the order of addition of the reactants (claim 1), so that the presently claimed process is encompassed by the teaching of document (3). Therefore, the Board considers, in agreement with both parties, that document (3) represents the closest state of the art and, hence, takes it as the starting point for assessing inventive step.

4.2 Having regard to this prior art, the Appellant submitted that the technical problem underlying the patent in suit was to provide a method for producing an amide improving the selectivity for the desired product, and improving thereby the yield of the reaction.

4.3 The solution to this problem proposed by the patent in suit is the method according to claim 1, which is characterized by the specific order of addition of the reactants, i.e. adding the carboxylic acid and the N-methylmorpholine to a solution of a carboxylic acid activating agent.

4.4 In order to demonstrate that the technical problem as defined above has effectively been solved by the claimed method the Appellant relied on the results observed in example 12 and comparative example 2 of the patent specification. According to example 12 the claimed process involving the required order of addition of reactants, i.e adding a substrate solution containing the acide and N-methylmorpholine to the

carboxylic acid activating agent isobutylcarbonate, achieves a yield of 96,0% of the desired amide. When reverting the order of addition of the reactants in comparative example 2, namely when adding the isobutylcarbonate to the acide and N-methylmorpholine the yield achieved is only 60.7%. It is thus credible that the claimed process which is characterized by the specific order of addition of the reactants improves the yield of desired product. The Board is thus satisfied that the technical problem as defined above is effectively solved by the claimed process.

The Respondent contested the fairness of the comparison arguing that during the work-up of the product the acidic treatment was not exactly the same in example 12 and in comparative example 2. In addition, the method used for determining the yield was also different. However, in both examples the obtained organic layer was treated with the same acid, i.e. hydrochloric acid which differed only in its concentration (1% versus 1.8%). In addition liquid chromatography was used for the determination of yields in both examples, although example 12 was carried out with high performance liquid chromatography whereas comparative example 2 involved silica gel liquid chromatography. The Respondent who contested the results observed and had thus the onus of proof of his allegation did not rely on any evidence substantiating that these minor differences have an impact on the yield obtained. In these circumstances, in the present case where a large difference of yield in the desired amide is observed, i.e. 60% according to the comparison versus 96% according to the invention, which represents an increase of about 50% in yield, the improvement shown by the Appellant is so large that it

remains credible irrespective of the above differences (see T 1711/06 not published in OJ EPO, point 3.5.2 of the Reasons). This argument of the Respondent must therefore be rejected.

4.5 It remains to be decided whether or not the proposed solution to that objective technical problem is obvious in view of the state of the art, in other words whether it was obvious for the person skilled in the art to change the order of addition of the reactants for improving the yield in desired product.

4.6 Document (2) which also relates to a method for producing amides by a process involving mixed anhydrides (column 1, lines 34 to 54) teaches that the addition of a carboxylic acid salt, i.e. the simultaneous addition of an acid and a base, to a solution of a carboxylic acid activating agent, namely chloroformate, provides *inter alia* the major advantage of increasing the yield of the desired end product, the amide (column 2, lines 1 to 12). Having regard to this prior art, it was obvious for the skilled person seeking to improve the yield of that desired end product to follow the order of addition of the reactants taught by document (2), i.e. adding the carboxylic acid and the base, i.e. N-methylmorpholine, to a solution of a carboxylic acid activating agent, arriving thereby without exercising inventive skill to the claimed solution.

4.6.1 According to the Appellant, the process described in the closest prior art document (3) required a base having a specific electronegativity, i.e inter alia N-methylmorpholine. Such bases were not disclosed in

document (2) which therefore could not suggest the claimed solution.

However, when starting from document (3) as the closest prior art, the skilled person does not have to select a base to arrive at the claimed solution since the base required by the claims in suit is already disclosed in the closest prior art and is not a feature characterizing the proposed solution. Hence, this argument must be rejected.

4.6.2 The Appellant also argued that document (5) taught that N-methylmorpholine was the preferred base for preparing mixed anhydrides but disclosed nevertheless only triethylamine as base when the order of addition of the reactants was the same as defined in the patent in suit. If it would have been obvious for the skilled person to use N-methylmorpholine with the order of addition of the reactants required by the patent-in suit this would have been disclosed in document (5) or at least later in document (3) which was from the same research group.

However, if document (3) had already disclosed the use of N-methylmorpholine in combination with the order of addition of the reactants as required by the patent in suit, it would not only be relevant for the matter of inventive step but it would destroy novelty. For the assessment of inventive step, a closest prior art document should be considered as it stands and cannot be artificially modified by reading an alleged teaching from another document into it. This line of argumentation of the Appellant amounts to mere speculation and has therefore to be rejected.

4.7 The Board concludes from the above that document (2) gives a clear incentive to the skilled person on how to solve the technical problem underlying the patent in suit, i.e. to improve the yield of desired end product, namely by adding the carboxylic acid and the base, i.e. N-methylmorpholine, to a solution of a carboxylic acid activating agent.

For these reasons, the subject matter of claim 1 lacks the required inventive step when combining the closest prior art illustrated by document (3) with the teaching of document (2) (Article 56 EPC). Consequently, this request has to be refused.

Main request and auxiliary request 1

5. The method according to claim 1 of the auxiliary request 5 is encompassed by claim 2 of the main request and claim 1 of the auxiliary request 1 which are both broader with regard to the definition of the reactants and prepared products. Therefore, the subject-matter of claim 2 of the main request and claim 1 of the auxiliary request 1 also lacks inventive step at least for the same reasons as given above (see point 4 *supra*). Consequently, the main request and the auxiliary request 1 have also to be rejected.

Auxiliary requests 2 and 3

6. When compared to claim 1 of the auxiliary request 5, claim 2 of the auxiliary request 2 and claim 1 of the auxiliary request 3 contain the additional feature requiring that the carboxylic acid and the base, i.e. N-methylmorpholine, are added "simultaneously". As

accepted by both parties this feature is taught by the closest prior art document (3) as well as by document (2) since in both documents the acid and the base can be added as a salt of the acid with the base, which implies that both components are added simultaneously (document (2), column 2, lines 1 to 4; document (3), example 7, column 9, lines 10 to 15). The parties conceded that this feature could thus not add any inventive ingenuity to the claimed process so that the findings and conclusions reached for the inventive activity of the subject matter of claim 1 of the auxiliary request 5 apply *mutatis mutandis* to the subject matter of claim 2 of the auxiliary request 2 and claim 1 of the auxiliary request 3 (see point 4 *supra*).

Hence, the process according to claim 2 of the auxiliary request 2 and claim 1 of the auxiliary request 3 does not involve an inventive activity and these requests have also to be rejected.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar The Chairman

C. Rodríguez Rodríguez R. Freimuth