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Datasheet for the decision of 20 May 2008

Case Number: T 1484/05 - 3.3.01

Application Number: 03744772.9

Publication Number: 1490353

IPC: C07D 401/14

Language of the proceedings: EN

Title of invention:
Method for manufacture of sertindole

Applicant:
H. LUNDBECK A/S

Opponent:
-

Headword:
Sertindole/LUNDBECK

Relevant legal provisions:
EPC Art. 56

Relevant legal provisions (EPC 1973):
-

Keyword:
"Inventive step (no) - obvious alternative process"

Decisions cited:
-

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1484/05 - 3.3.01

D E C I S I O N
of the Technical Board of Appeal 3.3.01
of 20 May 2008

Appellant: H. LUNDBECK A/S
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 23 June 2005 refusing European application No. 03744772.9 pursuant to Article 97(1) EPC 1973.**

Composition of the Board:

Chairman: P. Ranguis
Members: C. M. Radke
D. S. Rogers

Summary of Facts and Submissions

I. The appeal lies from the decision of the examining division refusing European patent application No. 03 744 772.9.

II. The following documents were cited during the examination procedure:

(1) J. Perregaard et al., J. Med. Chem., vol. 35 (1992), 1092-1101

(2) A. Klapars et al., J. Am. Chem. Soc., vol. 123 (2001), 7727-7729

III. The examining division decided that the subject-matter claimed did not involve an inventive step in view of documents (1) and (2).

In particular, it considered document (1) to represent the closest prior art. This document discloses that one may react 5-fluoro-, instead of 5-chloro-1*H*-indole, with 4-fluorohalobenzene. The examining division defined the problem to be solved by the present application as being the provision of an alternative process for making 5-chloro-indole derivatives.

The examining division pointed out that the skilled person knew from document (1) that Method A could be employed, if the substituted indole was commercially available (see page 1095, second paragraph). This was the case with 5-chloro-1*H*-indole. So the person skilled in the art would have reacted 5-chloro-1*H*-indole according to Method A as disclosed in document (1),

particularly since document (2) showed that the Ullmann reaction could be run with different starting compounds.

IV. The claims on file are claims 1-12 as originally filed.

Independent claims 1 and 2 read as follows:

"1. Method for manufacture of sertindole comprising manufacturing 5-chloro-1-(4-fluorophenyl)-indole and converting it to sertindole characterised in that the method for manufacture of 5-chloro-1-(4-fluorophenyl)-indole comprises reacting 5-chloro-indole with a 4-fluorophenylhalide in the presence of a base, a chelating ligand and catalytic amounts of a copper salt comprising copper(I) or copper(II) and an anion which does not interfere in an unfavourable way with the reaction."

"2. Method for manufacture of 5-chloro-1-(4-fluorophenyl)-indole comprising reacting 5-chloro-indole with a 4-fluorophenylhalide in the presence of a base, a chelating ligand and catalytic amounts of a copper salt comprising copper(I) or copper(II) and an anion which does not interfere in an unfavourable way with the reaction."

V. The Appellant argued that document (1) represented the closest prior art as it disclosed the preparation of 5-chloro-1-(4-fluorophenyl)-indole (i.e. the product prepared by the claimed processes) by Methods C and D.

In the Appellant's view the problem to be solved in the light of document (1) was to provide an alternative

process for making 5-chloro-1-(4-fluorophenyl)-indole that was amenable to scale-up.

When trying to solve this problem, the person skilled in the art would have started from Method C or D disclosed in document (1), and not from Method A, and thus would not have ended up with the process of the present claims.

VI. The Board summarised its preliminary and non binding opinion regarding inventive step in the communication dated 30 November 2007 annexed to the summons to oral proceedings. In this communication, the Board cited inter alia the following additional document and enclosed it in copy:

(4) Catalogue "Aldrich Katalog Handbuch Feinchemikalien und Laborgeräte", 2000-2001, Aldrich Chemie Deutschland, page 460

VII. By a letter dated 8 May 2008, the Appellant stated that he would not appear at the oral proceedings.

VIII. The Appellant requested in writing that the decision under appeal be set aside and that the case be remitted to the first instance with the order to grant a patent based on the application as originally filed.

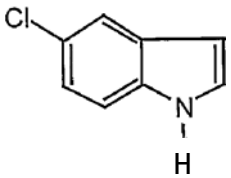
IX. Oral proceedings were held on 20 May 2008 in the absence of the Appellant (see Article 15(3) of the Rules of Procedure of the Boards of Appeal, OJ EPO 11/2007, 536). At the end of these proceedings, the decision of the Board was announced.

Reasons for the Decision

1. The appeal is admissible.

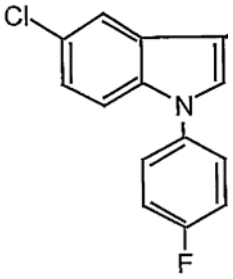
2. *Novelty*

The claims of the present application relate to chemical processes comprising the reaction of 5-chloro-1*H*-indole [I]



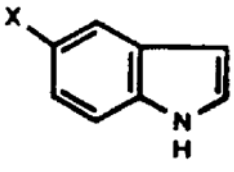
[I]

with a 4-fluorophenylhalide to yield 5-chloro-1-(4-fluorophenyl)-indole [II]



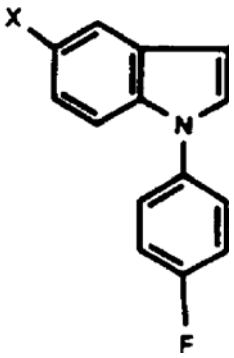
[II].

Document (1) teaches to react a compound of the formula [III]



[III]

where X = H, NO_2, CN or F,
with 1-fluoro-4-iodobenzene in the presence of K_2CO_3, CuBr and Cu bronze to yield compounds of the formula [IV]



[IV]

(see Method A in Scheme II and Table II, both on page 1094).

Neither document (1) nor any of the other documents cited above discloses the reaction of the compound of formula [I] (i.e. a compound of formula [III] with X = Cl) with a 4-fluorophenylhalide to yield 5-chloro-1-(4-fluorophenyl)-indole.

Therefore, the subject-matter of the present claims is novel.

3. *Inventive Step*

3.1 The Board agrees with the Appellant that document (1) represents the closest prior art. This document explicitly discloses the preparation of 5-chloro-1-(4-fluorophenyl)-indole by Method C or D (see compound 10h in Table II on page 1094), i.e. from a starting compound different than that of the formula [I] depicted under point 2 above.

3.2 The Appellant argued that the problem to be solved in view of document (1) was to provide an alternative process for making 5-chloro-1-(4-fluorophenyl)-indole, said process being "amenable to scale-up" (see the second paragraph of point V above).

Examples 4, 7, 10 and 31 of the application are covered by the claims and report conversions between 42 % and 45 % without specifying any yields or concentrations of side-products in the product mixture. There are no grounds for concluding that these examples of low conversion processes might be amenable to a scale-up, in addition the Appellant neither argued for, nor provided evidence to support such a conclusion. Consequently, the Appellant has not shown that the problem to provide an alternative process which is amenable to scale-up was solved over the whole breadth of the claims.

Hence, a less ambitious problem has to be formulated, namely to provide an alternative process for making 5-chloro-1-(4-fluorophenyl)-indole. The examples of the present application show that this problem is solved in view of document (1).

3.3 Then it has to be determined whether or not the person skilled in the art would have solved this problem by means of the features of the present claims, especially by those of independent claim 2.

3.3.1 The person skilled in the art looking for a process for making 5-chloro-1-(4-fluorophenyl)-indole by a process other than Methods C and D as disclosed in document (1) would realise from looking at Scheme II of this document that there are two alternative processes yielding 1-(4-fluorophenyl)-indoles, namely Methods A and B.

3.3.2 In document (1) it is preferred to prepare the 1-(4-fluorophenyl)-indoles by Method A whenever the respective 1*H*-indoles to be used as starting materials

"... were either **commercially available** at reasonable costs and quantities or if they could be conveniently prepared according to known methods."

(see page 1095, second paragraph; emphasis added by the Board).

Document (4) shows that 5-chloro-1*H*-indole - i.e. the indole derivative to be used as a starting compound in accordance with the present claims - was **commercially available** prior to the priority date of the present application (see compound "C4,760-4" on page 460 of document (4)).

Hence, the person skilled in the art could have used 5-chloro-1*H*-indole as a starting compound for making 5-chloro-1-(4-fluorophenyl)-indole according to method A as disclosed in document (1).

3.3.3 Document (1) mentions that "Certain indoles (10) are inaccessible or at least inconveniently prepared by methods A or B in large-scale quantities." (see page 1095, fourth paragraph).

However, the Board notes that said paragraph does not state that compound (10h), namely 5-chloro-1-(4-fluorophenyl)-indole, could not be made by Method A.

3.4 When considering Method A as an alternative to Methods C and D, the person skilled in the art would inform

himself on the type of reaction on which Method A is based, namely on the copper catalysed Ullmann arylation of indols (see document (1), page 1095, left column, lines 11-19). When doing so, he would take note of document (2).

3.4.1 Document (2) deals with copper catalysis in the N-arylation of nitrogen heterocycles such as indol and indol derivatives (see the title and Tables 2 and 3 on page 7728). This document was published about nine years later than document (1). It mentions that the Ullmann arylation was not employed to its full potential due to the high temperatures and often large amounts of copper reagent necessary up to then (see page 7727, right hand column, lines 1-5). In order to avoid these disadvantages, document (2) suggests to add "chelating nitrogen ligands" such as cyclohexanediamine to the copper reagent (namely CuI) and the base (see page 7727, right hand column, lines 8-19). Table 3 shows yields of 98 % or above for the N-arylation of indole or 5-substituted indoles with substituted phenyl iodides in the presence of the chelating ligand and 1 mol % CuI at 110°C (see compounds 4j-m and 4q).

3.4.2 These reaction conditions are less severe than those reported in document (1) (see page 1099, lines 7-28 where 40 mol % of CuBr are used and the reaction temperature is 180°C). Thus, the person skilled in the art would have realised that Method A according to document (1) would be a suitable alternative to Methods C and D if the catalyst was combined with the chelating agent recommended in document (2).

3.4.3 In view of these advantages, the person skilled in the art would have tried to prepare 5-chloro-1-(4-fluorophenyl)-indole with a reasonable expectation of success by Method A as disclosed in document (1) with the improved catalyst recommended in document (2), in spite of the fact that document (1) does not recommend this Method for the preparation of said product (see the Appellant's argument set out under point V above). Consequently, he would have modified Method A as disclosed in document (1) by adding a nitrogen chelating ligand as disclosed in document (2) to the copper salt and the base.

3.5 When doing this, he would have made use of all the features of present independent claim 2. For this reason, the subject-matter of this claim does not involve an inventive step.

3.6 The process of present claim 1 differs from that of claim 2 in that it additionally requires the conversion of the product of claim 2 to sertindole. This conversion is known from document (1) (see compound 14c in Table IV on page 1096 and page 1100, right hand column, third paragraph). Hence, the subject-matter of claim 1 is also not inventive, contrary to the requirements of Articles 52(1) and 56 EPC

4. Consequently the Board must reject the request of the Appellant to set aside the decision of the examining division refusing the application.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

M. Schalow P. Ranguis