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(21) International Application Number: PCT/FI92/00192 (22) International Filing Date: 18 June 1992 (18.06.92) (30) Priority data: 9113431.2 20 June 1991 (20.06.91) GB (71) Applicant (for all designated States except US): ORION-YH-TYMÄ OY [FI/FI]; Orionintie 1, SF-02100 Espoo (FI). (72) Inventors; and (75) Inventors/Applicants (for US only) : HONKANEN, Erkki [FI/FI]; Koivusyrjä 7 F, SF-02130 Espoo (FI). LINDHOLM, Stig [FI/FI]; Näyttelijäntie 16 H 82, SF-00400 Helsinki (FI).		(74) Agent: ORION CORPORATION; Orion-Farmos Pharmaceuticals, Patent Department, P.O. Box 65, SF-02101 Espoo (FI). (81) Designated States: AT, AU, BG, BR, CA, CH, CS, DE, DK, ES, FI, GB, HU, JP, KP, KR, LU, NL, NO, PL, RO, RU, SE, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE). Published <i>With international search report.</i>
(54) Title: METHOD FOR THE PREPARATION OF 3,4-DIHYDROXY-5-NITROBENZALDEHYDE		
(57) Abstract <p>A method for the preparation of 3,4-dihydroxy-5-nitrobenzaldehyde by reacting 4-hydroxy-3-methoxy-5-nitrobenzaldehyde with a strong nucleophilic agent which may be created by reacting an aromatic mercapto compound with a strong organic or inorganic alkali metal base such as lithium hydroxide. The reaction is performed at elevated temperatures using an aprotic polar solvent. It is preferably carried out in an inert atmosphere.</p>		

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Method for the preparation of 3,4-dihydroxy-5-nitrobenzaldehyde

5 The invention relates to a new method for the preparation of 3,4-dihydroxy-5-nitrobenzaldehyde, which is an intermediate in the synthesis of several pharmaceutically important catechol compounds.

10 GB-A-2200109 and EP 237929 describe a method for the preparation of 3,4-dihydroxy-5-nitrobenzaldehyde, in which method 4-hydroxy-3-methoxy-5-nitrobenzaldehyde is refluxed in concentrated hydrobromic acid. This method has many disadvantages which make it industrially inapplicable. For example, hydrobromic acid causes serious corrosion problems and results in the formation of the by-product 2-bromo-3,4-dihydroxy-5-nitrobenzaldehyde and dark coloured decomposition products which both interfere with the purification of the desired
15 3,4-dihydroxy-5-nitrobenzaldehyde. The emission of the toxic gaseous by-product methyl bromide is also a serious problem.

It has now been surprisingly found that the above disadvantages may be avoided if the dealkylation reaction is performed by using a strong nucleophilic reagent.
20 Preferably, the nucleophile is thiolate anion of an aromatic mercapto compound such as thiophenol, 2-, 3- or 4-aminothiophenol, 2-, 3- or 4-thiocresol or 1- or 2-thionaphthol. The thiolate anion is preferably created with the aid of a strong organic or inorganic base such as an alkali metal hydroxide, hydride or amide. Especially preferable are the lithium bases.

25 It is advisable to carry out the reaction in an inert atmosphere, thus preventing the formation of disulphide impurities. The reaction is preferably performed in an aprotic polar solvent, such as 1-methyl-2-pyrrolidinone, N,N-dimethylformamide or N,N-dimethylacetamide under reduced or normal pressure at elevated
30 temperature in the range of about 80 to 160, most preferably about 130 °C.

The reaction is very suitable for industrial production because the reagents are readily available, cheap, noncorrosive and easily handled. The solvent used can be easily recirculated and there is no emission of toxic gases.
35

Example 1

20 g of 4-hydroxy-3-methoxy-5-nitrobenzaldehyde, 5.4 g of lithium hydroxide, 12
5 ml of thiophenol and 40 ml of NMP (1-methyl-2-pyrrolidinone) were mixed for two
hours at 130 °C under nitrogen atmosphere. The mixture was cooled to 90 °C
and 125 ml of water, 40 ml of heptane and 30 ml of strong hydrochloric acid was
added. The mixture was stirred overnight at room temperature, kept for two hours
10 at 0 °C, filtered, washed with 20 ml of cold water and dried. Yield 16.52 g
(88.9 %), m.p. 135-137 °C.

Example 2

15 g of 4-hydroxy-3-methoxy-5-nitrobenzaldehyde, 4.1 g of lithium hydroxide, 9 ml
15 of thiophenol and 25 ml of NMP were mixed for two hours at 130 °C under
nitrogen atmosphere. The mixture was cooled to 100 °C and 50 ml of glacial
acetic acid and 30 ml of concentrated hydrochloric acid were added. The mixture
was stirred overnight at room temperature, kept for two hours at 0 °C, filtered,
washed with 20 ml of cold water and dried. Yield 11.38 g (81.7 %),
20 m.p. 135-137 °C.

Example 3

15 g of 4-hydroxy-3-methoxy-5-nitrobenzaldehyde, 3.7 g of lithium hydroxide, 13 g
25 of 2-mercaptobenzothiazole, 40 ml of NMP and 30 ml of toluene were refluxed
with water separation for 20 hours under nitrogen atmosphere. The mixture was
cooled to 80 °C and 150 ml of water and 20 ml of toluene were added. After
stirring for half an hour the phases were separated and the toluene phase
discarded. To the water phase 45 ml of concentrated hydrochloric acid was
30 added. The mixture was stirred overnight at room temperature, kept for two hours
at 0 °C, filtered, washed with 20 ml of cold water and dried. Yield 12.64 g
(90.7 %), m.p. 135-137 °C.

Example 4

150 g of 4-hydroxy-3-methoxy-5-nitrobenzaldehyde, 280 ml of NMP, 39 g of
5 lithium hydroxide and 90 ml of thiophenol were kept at 130 °C for three hours
under reduced pressure and the distillate was collected. The mixture was cooled
to 100 °C, the pressure normalized and 1000 ml of hot water and 250 ml of
concentrated hydrochloric acid were added. The mixture was stirred overnight at
room temperature, kept for two hours at 0 °C, filtered, washed with 200 ml of cold
10 water and dried. Yield 135 g (96.9 %), m.p. 135-137 °C.

CLAIMS

1. A method for the preparation of 3,4-dihydroxy-5-nitrobenzaldehyde comprising the reaction of 4-hydroxy-3-methoxy-5-nitrobenzaldehyde with a strong
5 nucleophilic agent.
2. The method according to claim 1, wherein the nucleophilic agent is created by reacting an aromatic mercapto compound with an alkali metal hydroxide, hydride or amide.
10
3. The method according to claim 2, wherein the aromatic mercapto compound is 2-mercaptobenzothiazole.
4. The method according to claim 2, wherein the aromatic mercapto compound is
15 thiophenol.
5. The method according to claim 2, wherein the said alkali metal is lithium.
6. The method according to claim 1, wherein it is performed in an inert
20 atmosphere.
7. The method according to claim 1, wherein it is performed in an aprotic polar solvent.
- 25 8. The method according to claim 7, wherein the aprotic polar solvent is 1-methyl-2-pyrrolidinone.
9. The method according to claim 1, wherein it is performed at the temperature from 80 to 160 °C.
30
10. The method according to claim 10, wherein it is performed at the temperature of about 130 °C.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/FI 92/00192

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC Int.Cl. 5 C07C205/44; C07C201/12		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	C07C	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
Y	GB,A,2 200 109 (ORION - YHTYMA OY) 27 July 1988 cited in the application see example 111 ---	1-10
Y	SYNTHESIS. no. 3, 1976, STUTTGART DE pages 191 - 192; C. HANSSON ET AL.: 'Selective Dealkylation of Activated Aromatic Ethers.' see the whole document ---	1-10
A	TETRAHEDRON LETTERS. no. 16, 1970, OXFORD GB pages 1327 - 1328; G.I. FEUTRILL ET AL.: 'Demethylation of Aryl Methyl Ethers with Thioethoxide ion in Dimethyl Formamide.' see the whole document ---	1
<p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
21 SEPTEMBER 1992	14. 10. 92	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	BONNEVILLE E. I.	

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. FI 9200192
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This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		BE-A- 1003279	18-02-92
		DE-A- 3740383	01-06-88
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		JP-A- 63170311	14-07-88
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		NL-A- 8702857	16-06-88
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		ZA-A- 8708953	24-05-88
