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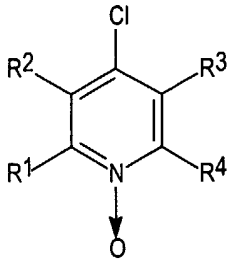
(54) Title: PROCESS FOR THE PREPARATION OF 4-CHLOROPYRIDINE-N-OXIDES

(57) Abstract: Process for the preparation of a 4-chloropyridine-N-oxide of formula (1) in which R^1, R^2 and R^3 each independently stand for H, an alkyl group or an alkoxy group and R^4 stands for an alkyl group or an alkoxy group, in which the corresponding 4-H-pyridine-N-oxide is subjected to a treatment with Cl_2, resulting in the formation of 4-Cl-pyridine-N-oxide. Preferably R^1 stands for H, R^2 stands for H or methyl, and R^3 and R^4 both stand for CH_3, or R^1 and R^2 both for H, R^3 for methoxy and R^4 for methyl. Preferably the chlorination is carried out in the presence of a base, for example an (earth) alkali metal hydroxide or carbonate, and water, and use is made of between 1 and 3 base equivalents, calculated relative to the quantity of 4-H-pyridine-N-oxide and 0 to 10 equivalents of water, calculated relative to the quantity of 4-H-pyridine-N-oxide. The 4-Cl-pyridine-N-oxide obtained can subsequently be subjected to a treatment with a substituted or unsubstituted alcohol in the presence of a base. The resulting compounds are suitable for use in the preparation of pharmaceuticals, for example omeprazol, pantoprazol, rabeprazol and lansoprasol.

PROCESS FOR THE PREPARATION OF 4-CHLOROPYRIDINE-N-OXIDES

The invention relates to a process for the preparation of 4-chloropyridine-N-oxide of formula (1)



(1)

In which R^1, R^2 en R^3 each independently stand for H, an alkyl group or an alkoxy group and R^4 stands for an alkyl group or an alkoxy group, in which the corresponding 4-H-pyridine-N-oxide is subjected to a treatment with Cl_2, resulting in the formation of the 4-Cl-pyridine-N-oxide.

4-Cl-pyridine-N-oxides can be used as intermediate products in the preparation of important pharmaceuticals such as omeprazol, pantoprazol, rabeprazol and lansoprazol. As a rule this involves their conversion into 4-alkoxy-pyridine-N-oxides, for example 4-methoxy-2,3,5-trimethyl-pyridine, 3,4-dimethoxy-2-methyl-pyridine, 4-(3-methoxy-propyloxy) or 4(2-trifluorethyl)2,3-dimethylpyridine.

In the literature various processes are described for the chlorination of 4-H-pyridine-N-oxides. GB-A-958877, for example, describes the treatment of 4-H-pyridine-N-oxides with a combination of Cl_2 and SO_2. KR-B-9106983 describes the chlorination of 4-H-2,3,5-trimethylpyridine-N-oxide with $POCl_3$, resulting in the formation of 4-Cl-2,3,5-trimethylpyridine. The 4-Cl-pyridine obtained is subsequently oxidized to form the corresponding pyridine-N-oxide after which the 4-methoxy-2,3,5-trimethyl-pyridine-N-oxide is obtained with the aid of methanol and a base.

A disadvantage of the known processes is that the pyridine N-oxide is reduced in the chlorination, so that for the subsequent steps to 4-alkoxy or 4-aryloxy substituted pyridines an extra oxidation step is necessary to obtain the corresponding pyridine N-oxide.

Another known route for the preparation of 4-Cl-pyridine-

N-oxides is described in US-A-5045552. In the route described here the 4-Cl-pyridine-N-oxide is prepared from the corresponding 4-nitro-pyridine-N-oxide with the aid of acetyl chloride. A disadvantage of this route is that the 4-nitro-pyridine-N-oxides obtained as intermediates are relatively explosive and are suspected carcinogens.

Examples of suitable compounds that can be prepared with the process according to the invention are 4-chloro-pyridine-N-oxides of formula (1) where R^1, R^2 and R^3 stand for H, an alkyl group with 1-3 C atoms or an alkoxy group with 1-3 C atoms, and where R^4 stands for an alkyl group with 1-3 C atoms or an alkoxy group with 1-3 C atoms. Preferably R^3 and R^4 each independently stand for an alkyl group or an alkoxy group, R^1 stands for H and R^2 for H, an alkyl group or an alkoxy group, most preferably $R^3 = R^4 = CH_3$, R^2 = H or CH_3 and R^1 = H, or $R^1 = R^2$ = H, $R^3 = OCH_3$ and $R^4 = CH_3$. The alkyl and or alkoxy groups in R^1, R^2, R^3 or R^4 may optionally be substituted .

The temperature at which the chlorination takes place is not very critical and for example lies between -20 and 100 °C, preferably between 10 and 50°C. The pressure at which the reaction is carried out may in practice for example lie between 0.1 and 10 MPa. For practical reasons atmospheric pressure will often be chosen where possible. Higher pressures are advantageous for keeping Cl_2 gas in solution.

If desired the chlorination reaction can be carried out in a solvent. As solvent in principle all solvents can be considered in which the reactants dissolve to an acceptable degree and that are inert under the reaction conditions. Examples of suitable solvents are halogenated hydrocarbons, in particular dichloromethane or dichlorobenzene and alkane carboxylic acids with for example 1-10 C atoms, in particular acetic acid.

The quantity of chlorine gas applied is preferably larger than 0.5 equivalent, calculated relative to the quantity of 4-H-pyridine-N-oxide. When less than 1 equivalent of chlorine gas is applied the non-converted 4-H-pyridine-N-oxide is preferably recycled. For optimum conversion use is preferably made of more than 1 equivalent of chlorine gas, calculated relative to the quantity of 4-H-pyridine-N-oxide. The optimum excess depends for example on the quantity of dichloropyridine-N-oxide that can be formed, for example when R^1, R^2 and/or R^3 represent hydrogen. This optimum can easily be determined by one skilled in the art for his specific situation.

Preferably the reaction is carried out with chlorine gas in the

presence of a base. As a result a higher conversion is reached. Suitable bases that can be applied are for example (earth) alkali metal hydroxides or carbonates and alkali metal salts, in particular Na or K, of carboxylic acids, in particular sodium acetate. The quantity of base to be applied preferably lies between 0.5 and 10 equivalents, calculated relative to the quantity of 4-H-pyridine-N-oxide, in particular between 1 and 3 equivalents.

Preferably the chlorination reaction is carried out in the presence of water. The quantity of water preferably lies between 0 and 10 equivalents, calculated relative to the quantity of 4-H-pyridine-N-oxide. As more water is present in the reaction mixture, more chlorine bleach liquor can be formed, which may adversely affect the reaction.

After the chlorination reaction the resulting 4-Cl-pyridine-N-oxide can, if desired after recovery, be used in the preparation of the corresponding N-alkoxy-pyridine or N-aryloxy-pyridine. This involves contacting the 4-Cl-pyridine-N-oxide with the alcohol corresponding to the alkoxy or aryloxy group, for example methanol, methoxypropanol or 2-trifluorethanol, in the presence of a base. If desired this reaction can be carried out in a solvent. Suitable bases that can be applied in the preparation of the 4-alkoxy-pyridine-N-oxide are for example alkali metals and alkali metal hydroxides, hydrides or alcoholates, where alkali metal generally stands for Na or K. Examples of suitable solvents that can be applied if desired are aromatic hydrocarbons, in particular toluene or xylene; ethers, for example tetrahydrofuran (THF); dimethyl formamide (DMF) or dimethyl sulfoxide (DMSO). The temperature at which the reaction is carried out is not critical and for example lies between -20 °C and the boiling point of the chosen solvent, preferably between 0 and 140 °C.

In a number of cases a mixture of particularly corresponding 4-Cl-pyridine-N-oxide and 2-Cl-pyridine-N-oxide is formed in the chlorination. These products can be separated if desired, for example by crystallization or chromatography.

The invention will now be explained on the basis of the examples, without however being limited thereby.

Example

Preparation of 4-chloro-2,3-lutidine-N-oxide (4-chloro-2,3-dimethyl-pyridine-N-oxide)

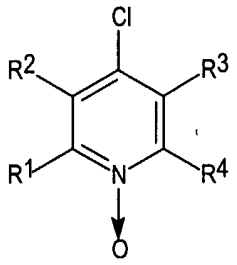
Chlorine gas (100 g; 1.4 mol) was introduced for 2-3 hours into a solution of 2,3-Lutidine-N-oxide (343.4 g; 2.79 mol) in dichloromethane (1200 ml) which was meanwhile being stirred and cooled (25-30 °C). When the conversion had reached approx. 50% the introduction of chlorine was stopped and 50% sodium hydroxide solution (223.2 g; 2.79 mol) was metered in 1 hour while cooling (<30 °C). Subsequently chlorine gas (100 g; 1.4 mol) was again introduced for 3-4 hours at 25-30 °C until the conversion was >98%.

Water (400 ml) was added to the reaction mixture and the salts that were present were dissolved while the mixture was being stirred. The phases were separated and the pH was adjusted with 50% sodium hydroxide solution (55.3 g) until the pH=6.7. The aqueous phase was twice extracted with dichloromethane (100 ml each).

The combined organic phases, containing 311.7 g (1.98 mol= 70.9%) 4-chloro-2,3-lutidine-N-oxide, were concentrated by distillation off 1000 ml of dichloromethane. Subsequently 1000 ml ethyl acetate was dosed at 45-50 °C. The mixture was cooled and crystallization occurs. The mixture was stirred at 10-15 °C, the solids were filtered off, washed twice with 150 ml ethyl acetate and dried (yield 207 g; 47.1%)

CLAIMS

1. Process for the preparation of 4-chloropyridine-N-oxide of formula (1)



(1)

in which R^1, R^2 and R^3 each independently stand for H, an alkyl group or an alkoxy group and R^4 stands for an alkyl group or an alkoxy group, in which the corresponding 4-H-pyridine-N-oxide is subjected to a treatment with Cl_2, resulting in the formation of 4-Cl-pyridine-N-oxide.

2. Process according to claim 1 in which R^3 and R^4 each independently stand for an alkyl group or an alkoxy group, R^1 stands for H and R^2 stands for H, an alkyl or an alkoxy group.

3. Process according to claim 2 in which R^2 stands for H or methyl, and R^3 and R^4 both stand for CH_3.

4. Process according to claim 2 in which R^2 stands for H, R^3 for methoxy and R^4 for methyl.

5. Process according to one of the claims 1-4, in which the chlorination is carried out in the presence of a base.

6. Process according to claim 5 in which an (earth) alkali metal hydroxide or carbonate is applied as a base.

7. Process according to claim 5 or 6, in which the quantity of base applied lies between 1 and 3 equivalents, calculated relative to the quantity of 4-H-pyridine-N-oxide.

8. Process according to one of the claims 1-7, in which the chlorination reaction is carried out in the presence of water.

9. Process according to one of the claims 1-8, in which the quantity of water lies between 0 and 10 equivalent, calculated relative to the quantity of 4-H-pyridine-N-oxide.

10. Process according to claim 1 or 2, wherein the 4-Cl-pyridine-N-oxide

obtained is subjected to a treatment with a substituted or unsubstituted alcohol in the presence of a base.

11. Use of the compounds obtained in the process according to any one of claims 1-10 in the preparation of pharmaceuticals, for example omeprazol, pantoprazol, rabeprazol and lansoprasol.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/NL 02/00379

A. CLASSIFICATION OF SUBJECT MATTER
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BEILSTEIN Data, CHEM ABS Data, EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	GB 958 877 A (LEUNA WERKE VEB) 27 May 1964 (1964-05-27) cited in the application examples	1

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
4 September 2002	11/09/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bosma, P

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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