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(54) Title: METHOD FOR PREPARING 2-CHLOROPROPIONALDEHYDE AND USE OF THE SAME

(57) **Abstract:** A method of preparing 2-chloropropionaldehyde at a high yield from propionaldehyde and chlorine by a simple procedure of continuously or intermittently supplying a mixture of an equivalent mol of these two compounds to the reactor and reacting at -30 to 30°C. An aqueous solution containing 2-chloropropionaldehyde can be extracted with water from the chlorination reaction product at a high yield. In addition, 2-amino-5-methylthiazole can be prepared at a high yield by the cyclocondensation reaction by the addition of thiourea to the aqueous solution containing 2-chloropropionaldehyde.

DESCRIPTION

METHOD FOR PREPARING 2-CHLOROPROPIONALDEHYDE AND USE OF THE SAME

TECHNICAL FIELD

The present invention relates to a method for preparing 2-chloropropionaldehyde which is useful as an intermediate compound for agricultural chemicals and pharmaceuticals.

The present invention further relates to a method for preparing 2-amino-5-methylthiazole, which is useful as an intermediate compound for agricultural chemicals and pharmaceuticals, using 2-chloropropionaldehyde obtained by the above method.

BACKGROUND ART

Among the methods of preparing of 2-chloropropionaldehyde, there are following reports concerning preparation of 2-chloropropionaldehyde by the reaction of propionaldehyde and chlorine.

Japanese Patent Application Laid-open No. 173785/1992 (corresponding to EP 484742) describes a process comprising injecting 0.76 mol of chlorine to 1 mol of propionaldehyde at a reaction temperature of 5±1°C, adding benzene to the resulting chlorination reaction solution, and subjecting the mixture to azeotropic distillation, thereby producing a benzene solution containing 2-chloropropionaldehyde at an yield of 73% on the basis of chlorine (56% on the basis of propionaldehyde).

Dick reported that 2-chloropropionaldehyde was obtained in 92% yield, if an increase of HCl concentration in the reaction mixture due to HCl by-produced in the reaction is controlled at 6 N by the addition of water, when chlorine is injected to a propionaldehyde solution in a 6 N hydrochloric acid solution (J. Org. Chem., 27, 272-274 (1962); the same chlorination method is also described in USP 3,240,813 to Dick).

Although the chlorination method of Dick is utilized by Gaydou (Bull. Soc. Chim. Fr., (French), 2275-2278 (1973)) and Metcalf et al. (J. Agric. Food Chem., 25, 859-868 (1977) and Japanese Patent Application Laid-open No. 70813/1976 (corresponding to GB 1529575), these prior art documents do not describe the reproducibility of yields.

These prior art documents only have made it clear that there was still a strong desire for a method of preparing 2-chloropropionaldehyde by a simple method at a high yield with excellent reproducibility.

There are the following reports dealing with the method for preparing 2-amino-5-methylthiazole.

Wakasugi et al. reported that 2-amino-5-methylthiazole was obtained from 2-chloropropionaldehyde and thiourea in 78% yield by cyclocondensation while heating in toluene (Chemistry Letters, 1994, 2039-2042).

Nagasawa reported that 2-amino-5-methylthiazole was obtained in 48% yield by cyclocondensation of 2-bromopropionaldehyde diethyl acetal and thiourea while heating in water (Yakugaku Zasshi, 60, 433-441 (1940); Chem. Abstr., 458 (1941)).

McLean et al. reported that 2-amino-5-methylthiazole was obtained in 69% yield by cyclocondensation of 2-bromopropionaldehyde hydrate and thiourea while heating (J. Chem. Soc., 1942, 383-386).

Kulkarni et al. reported that 2-amino-5-methylthiazole was obtained in 79% yield by cyclocondensation of chlorinated propyl alcohol and thiourea while heating in water (J. Sci. Industr. Res., 18B, 411-413(1959)).

All methods described in the above four prior art documents have problems still to be improved in the method for preparing raw materials and the yield of the target product.

The present inventors have conducted extensive studies concerning the method for synthesizing 2-chloropropionaldehyde by the reaction of propionaldehyde and chlorine at a high yield, and the method for synthesizing 2-amino-5-methylthiazole at a high yield by the reaction of 2-chloropropionaldehyde thus obtained and thiourea.

DISCLOSURE OF THE INVENTION

An object of the present invention is to provide a method of preparing 2-chloropropionaldehyde which comprises reacting propionaldehyde and chlorine at a temperature between -30 and 30°C while continuously or intermittently, preferably continuously supplying these compounds to a reactor at an almost equivalent mol ratio in a small amount at a time.

Another object of the present invention is to provide a method of preparing an aqueous solution containing 2-chloropropionaldehyde which comprises reacting propionaldehyde and chlorine at a temperature between -30 and 30°C while continuously or intermittently, preferably continuously supplying these compounds to a reactor at an almost equivalent mol ratio in a small amount at a time, adding water to the reaction mixture, extracting the resulting mixture at a temperature between -20 and 50°C, and separating the water layer from the oil layer.

Still another object of the present invention is to provide a method of preparing 2-amino-5-methylthiazole which comprises adding thiourea to the aqueous solution containing 2-chloropropionaldehyde obtained by the above-mentioned method and reacting the mixture at a temperature between 20 and 120°C.

BEST MODE OF FOR CARRYING OUT THE INVENTION

The first invention is a method of preparing 2-chloropropionaldehyde by continuously or intermittently, preferably continuously supplying propionaldehyde and chlorine to a reactor at an almost equivalent mol ratio in a small amount at a time and reacting these compounds (hereinafter called "simultaneous small amount addition chlorination method").

Propionaldehyde and chlorine manufactured by common methods can be used as the raw materials for the simultaneous small amount addition chlorination method. Because the target reaction is an equivalent molar reaction, the reaction raw material propionaldehyde and chlorine are preferably used in an equimolar amount both during and after the reaction.

In the event that either raw material is supplied in an excessive amount during the continuous reaction, the amount successively or intermittently, preferably successively supplied should preferably be adjusted so that an equimolar supply may be restored as quickly as possible. The chlorination reaction temperature is between -30 and 30°C, preferably between -20 and 20°C, and more preferably between -15 and 15°C.

Here, a small amount supply means that the amount of unreacted propionaldehyde remaining in the reaction mixture while the raw materials are continuously or intermittently, preferably continuously supplied is controlled to 10 wt% or less, preferably 5wt% or less, and more preferably between 1 and 3 wt% of the reaction mixture. If the amount of unreacted propionaldehyde is more than 10 wt%, by-products with a boiling point higher than the boiling point of 2-chloropropionaldehyde are easily produced, resulting in a decrease in the yield.

On the other hand, if an excess chlorine is supplied to the reactor, polychlorides tend to be easily produced, which also results in a decrease in the yield.

In this manner, production of 2-chloropropionaldehyde at a high yield as compared with a conventional chlorination method, in which chlorine is injected into propionaldehyde, can be ensured by continuously or intermittently, preferably continuously supplying raw materials simultaneously in a small amount at a time while controlling the chlorination temperature and maintaining the concentration of unreacted raw materials within a certain range. Furthermore, a drastic chlorination reaction after a certain induction period and resulting production of a large amount of by-products, which is difficult to control and affects the production yield, as experienced in a conventional chlorination reaction wherein chlorine is injected to propionaldehyde, can be avoided.

It is desirable to add 2-chloropropionaldehyde and/or an appropriate solvent to the reactor previously when the reaction is initiated so that the concentration of unreacted propionaldehyde within a certain range may be maintained.

Although separately prepared 2-chloropropionaldehyde may be used as 2-chloropropionaldehyde which is present in the reactor in advance, 2-chloropropionaldehyde may be produced by charging a prescribed amount of propionaldehyde in the reactor, cooling it to -6°C, adding 36% hydrochloric acid solution to trimerize about 1/4 amount of the propionaldehyde by cyclization while maintaining the temperature below 20°C, then effecting a chlorination reaction. 2-chloropropionaldehyde thus produced may be separated from the reaction mixture and is used as 2-chloropropionaldehyde to be present in the reactor in advance. However, it is possible to continuously feed propionaldehyde and chlorine gas in a small amount at a time to the reactor in which the above reaction products are present without being separated, thereby manufacturing 2-chloropropionaldehyde.

When 2-chloropropionaldehyde which is caused to be present in the reactor in advance is prepared by a method of injecting chlorine into propionaldehyde, about 20-30% of by-products which have a boiling point higher than the boiling point of 2-chloropropionaldehyde and are scarcely soluble in water can be produced. However, if the simultaneous small amount addition chlorination method is carried out in the presence of the above reaction mixture, there is almost no increase in the amount of by-products having a boiling point higher than that of 2-chloropropionaldehyde and scarcely soluble in water.

Chloroform, carbon tetrachloride, ethylene dichloride, and the like can be given as examples of suitable solvents which are chlorinated only with difficulty used in place of or together with 2-chloropropionaldehyde.

The second invention is a method of preparing an aqueous solution containing 2-chloropropionaldehyde which comprises reacting propionaldehyde and chlorine while continuously or intermittently, preferably continuously supplying these compounds to a reactor at an almost equivalent mol ratio in a small amount at a time, adding water to the reaction mixture, extracting the resulting mixture, and separating the water layer from the oil layer.

In the preparation of an aqueous solution containing 2-chloropropionaldehyde, the reaction mixture which can be obtained by the above-mentioned simultaneous small amount addition chlorination method can be used as it is.

The reaction mixture obtained by chlorination of propionaldehyde is maintained at a temperature between -20 and 50°C, preferably between -10 and 30°C, and more preferably between 0 and 30°C, water is added, and the resulting mixture is extracted in 0.2 to 4 hours and allowed to stand for 0.2 to 4 hours to separate a water layer from an oil layer, thereby obtaining an aqueous solution containing 2-chloropropionaldehyde as the water layer. Usually, the oil layer is again subjected to an extraction operation.

When approximately the same amount of water as the reaction mixture is used for the extraction, for example, the oil layer separated in the first extraction operation is subjected to extraction one or two more times, whereby the aqueous solution containing 2-chloropropionaldehyde can be obtained at a high yield. An aqueous solution with a concentration of 30-50 wt%, which is a suitable concentration for the succeeding reaction, can be obtained efficiently by suitably designing the amount of water and the extraction method.

An easy separating operation of the oil layer which is a highly acidic and difficult-to-handle by-product is a feature of the second invention.

Because the method of preparing an aqueous solution containing 2-chloropropionaldehyde of the present invention by extracting the reaction mixture obtained by the simultaneous small amount addition chlorination method with water has an advantage of eliminating impurities as a residual oil layer, this method is applicable to reaction mixtures other than that obtained by the simultaneous small amount addition chlorination method, such as a reaction mixture of propionaldehyde and chlorine.

The third invention is a method of preparing 2-amino-5-methylthiazole by adding thiourea to an aqueous solution containing 2-chloropropionaldehyde and reacting the mixture at a temperature between 20 and 120°C. This method is hereinafter called "a method of preparing 2-amino-5-methylthiazole by the use of an aqueous medium".

In the method of preparing 2-amino-5-methylthiazole by the use of an aqueous medium, the aqueous solution containing 2-chloropropionaldehyde obtained by water extraction of the reaction mixture which is prepared by the simultaneous small amount addition chlorination method can be used as the raw material aqueous solution containing 2-chloropropionaldehyde.

2-amino-5-methylthiazole can be prepared by the cyclocondensation reaction of 2-chloropropionaldehyde and thiourea at a high yield by adding thiourea to the aqueous solution containing 2-chloropropionaldehyde obtained in the above method in an amount from 0.5 to 2.0 mols, preferably from 0.8 to 1.2 mols, and more preferably from 0.9 to 1.1 mols for one mol of 2-chloropropionaldehyde, and reacting these compounds at a temperature sufficient to complete the reaction in a period of time from 0.3 to 24 hours, preferably from 0.5 to 20 hours, and more preferably from 1 to 15 hours, specifically, at a temperature from 20 to 120°C, preferably from 30 to 110°C, and more preferably from 40 to 100°C.

As a method for isolating 2-amino-5-methylthiazole, a method of neutralizing the cyclocondensation reaction mixture to precipitate 2-amino-5-methylthiazole, followed by filtration, washing, and drying, can be given. High purity 2-amino-5-methylthiazole can be obtained by this simple isolation procedure.

Thus, preparation of high purity 2-amino-5-methylthiazole at a high yield by a simple procedure is a feature of the third invention.

Because of the use of water as a solvent, the method of preparing 2-amino-5-methylthiazole by the use of an aqueous medium according to the third invention has not only an advantage of a high yield, but also an advantage of avoiding the danger which may be caused by the use of an organic solvent. Therefore, this method is applicable to the cyclocondensation of 2-chloropropionaldehyde, which is obtained by a method other than that from an aqueous solution containing 2-chloropropionaldehyde prepared from the reaction mixture obtained by the simultaneous small amount addition chlorination method, and thiourea in an aqueous medium, preferably in the presence of an acid catalyst (usually, hydrochloric acid).

2-Amino-5-methylthiazole is known to be useful as a compound which can be converted to an intermediate for insecticidal compounds (for example, Japanese Patent Application Laid-open No. 202778/1997(corresponding to EP 775700)). 2-Chloro-5-chloromethylthiazole, for example, which is known to be useful as a compound for preparing an intermediate for an insecticidal compound, can be prepared from 2-amino-5-methylthiazole via the following two steps.

In the first step, the 2-amino group of 2-amino-5-methylthiazole is converted into a 2-chloro group via a 2-diazonium group, thereby producing 2-chloro-5-methylthiazole (this step is hereinafter called "a nuclear chlorination step").

In the second step, 2-chloro-5-methylthiazole is chlorinated by N-chlorosuccinimide in the presence of a radical initiator and/or by irradiation of UV rays, to synthesize 2-chloro-5-chloromethylthiazole (this step is hereinafter called "a side chain chlorination step").

The nuclear chlorination step is operated as follows.

An aqueous solution containing 2-amino-5-methylthiazole and hydrogen chloride in an amount of 2.3-10 mols, preferably 2.7-8 mols, and more preferably 3-6 mols per one mol of 2-amino-5-methylthiazole is prepared. To this aqueous solution, an aqueous solution containing sodium nitrite in an amount of 0.7-1.5 mols, preferably 0.9-1.4 mols, and more preferably 0.95-1.2 mols per one mol of 2-amino-5-methylthiazole is added dropwise at a temperature from -30 to 40°C, preferably from -20 to 30°C, and more preferably from -10 to 10°C. After the addition, the mixture is stirred for 0.2 to 3 hours, preferably for 0.3 to 2 hours, and more preferably for 0.5 to 1.5 hours.

Then, the diazotization reaction mixture is reacted at a temperature from 20 to 100°C, preferably from 30 to 90°C, and more preferably from 40 to 80°C for 12 minutes to 6 hours, preferably for 0.5 to 4 hours, and more preferably for 1 to 3 hours to replace 2-diazonium groups with chlorine ions, thereby producing 2-chloro-5-methylthiazole. As clear from the above-described method, if 2-amino-5-methylthiazole is synthesized as an aqueous solution at a high yield, 2-amino-5-methylthiazole can be advantageously used without isolation.

EXAMPLES

The following preparation examples of the present invention will now be described in more detail.

* A preparation example of 2-chloropropionaldehyde by the simultaneous small amount addition chlorination method.

* A preparation example of an aqueous solution containing 2-chloropropionaldehyde by extraction of the reaction mixture of the simultaneous small amount addition chlorination method with water.

* A preparation example of 2-amino-5-methylthiazole by the cyclocondensation reaction by the addition of thiourea to the aqueous solution containing 2-chloropropionaldehyde

* A preparation example of 2-chloro-5-methylthiazole from the 2-amino-5-methylthiazole thus prepared.

Reference Preparation Example 1

<Synthesis of 2-chloropropionaldehyde>

A 1 litter four-necked flask equipped with a stirrer, dropping funnel, chlorine introduction tube, thermometer, and condenser was charged with 101.4 g (1.75 mol) of propionaldehyde which was purified by distillation, followed by cooling to -6°C. A cyclization-trimerization reaction was carried out by adding 2.8 g of 36% hydrochloric acid while maintaining the mixture at 20°C or below. The ratio of propionaldehyde and its cyclic trimer 1.5 hours after the addition was 75:25.

Next, chlorine gas was fed for one hour at a rate of 0.05 l/min while maintaining the reaction solution at 10°C or less, then for 2.5 hours at a rate of 0.25 l/min at 0°C or less. The content of 2-chloropropionaldehyde at this point of time was 120.5 g (1.30 mol) (yield 74.3%).

Preparation Example 1

<Synthesis of 2-chloropropionaldehyde>

The following reaction was carried out using the mixture and equipment of the Reference Preparation Example 1. While maintaining the mixture at 0°C or less, propionaldehyde and chlorine gas were fed for 2 hours and 20 minutes at a rate of 1.0 ml/min (total of 110.0 g, 1.89 mol) and 0.3 l/min, respectively. Chlorine gas was fed short time to adjust the composition, to obtain 412.6 g of a chlorination solution which contains 285.6 g (3.08 mol)of 2-chloropropionaldehyde. The yield of 2-chloropropionaldehyde by the application of the simultaneous small amount addition chlorination method after that was 94.2%.

Preparation Example 2

<Preparation of an aqueous solution containing 2-chloropropionaldehyde>

412.6 g of water was added to the reaction mixture obtained in Preparation Example 1 while maintaining this mixture at 20°C or below, and the resulting mixture was stirred to extract 2-chloropropionaldehyde in the water layer. After stirring the mixture was transferred to a 1 liter separating funnel to separate the water layer (upper layer) from the oil layer (lower layer). The oil layer was extracted again with 412.6 g of water. The amount of 2-chloropropionaldehyde which was extracted in the water layer in the two extraction operation was 266.2 g (2.88 mol), and the extraction yield was 93.2%.

Preparation Example 3

<Preparation of 2-amino-5-methylthiazole>

A 2 litter four-necked flask equipped with a stirrer, thermometer, and condenser was charged with the extracted solution obtained in the Preparation Example 2. 0.98 time mol of thiourea in the amount of 214.7 g (2.82 mol) was added and the mixture was stirred. The reaction solution was heated to 60-80°C and reacted for 3 hours, followed by cooling to room temperature. Next, the reaction solution was neutralized by dropping 25% sodium hydroxide aqueous solution, thereby obtaining crystals of 2-amino-5-methylthiazole. The amount of 2-amino-5-methylthiazole obtained after vacuum drying was 296.4 g (2.60 mol) and the yield on the basis of thiourea was 92.0%. The yield on the basis of 2-chloropropionaldehyde was 90.2%.

Reference Preparation Example 2

<Preparation of 2-chloro-5-methylthiazole>

A 3 litter four-necked flask equipped with a stirrer, thermometer, condenser, and dropping funnel was charged with 296.4 g (2.60 mol) of 2-amino-5-methylthiazole and 908 ml of 35% hydrochloric acid (10.4 mol as HCl), and the mixture was stirred. After cooling to -5°C, 500 g of an aqueous solution containing 197.4 g (2.86 mol) of sodium nitrite was slowly dropwise added while maintaining the reaction temperature at 0°C or below. After dropping, the mixture was stirred for one hour at a temperature of 0°C or below, followed by heating at 60°C. After stirring for a further one hour at 60°C, the mixture was cooled to room temperature. 800 ml of chloroform was added to this reaction solution in three portions to extract 2-chloro-5-methylthiazole. After removing chloroform, the mixture was distilled under reduced pressure to obtain 284.4 g (2.13 mol) of 2-chloro-5-methylthiazole. The yield on the basis of 2-amino-5-methylthiazole was 82%.

INDUSTRIAL APPLICABILITY

2-Chloropropionaldehyde can be prepared at a high yield by the chlorination method of the present invention in which propionaldehyde and chlorine gas are simultaneously supplied. In addition, an aqueous solution containing 2-chloropropionaldehyde can be extracted from the reaction product with water at a high yield.

Moreover, 2-amino-5-methylthiazole can be prepared at a high yield by the cyclocondensation reaction which is effected by the addition of thiourea to the aqueous solution containing 2-chloropropionaldehyde. The 2-amino-5-methylthiazole thus obtained can be easily converted into an intermediate such as 2-chloro-5-methylthiazole which is useful for the preparation of pharmaceuticals and agricultural chemicals.

CLAIMS:

1. A method of preparing 2-chloropropionaldehyde comprising reacting propionaldehyde and chlorine at a temperature from -30°C to 30°C while continuously or intermittently supplying these compounds to a reactor in a small amount at a time.

2. The method according to claim 1, wherein the propionaldehyde is supplied at a rate so that unreacted propionaldehyde in the reaction solution is maintained 10 wt% or less.

3. A method of preparing an aqueous solution containing 2-chloropropionaldehyde which comprises reacting propionaldehyde and chlorine at a temperature between -30 and 30°C while continuously or intermittently supplying these compounds to a reactor in a small amount at a time, adding water to the reaction mixture, extracting the resulting mixture at a temperature between -20 and 50°C, and separating the water layer from the oil layer.

4. The method according to claim 3, wherein the propionaldehyde is supplied at a rate so that unreacted propionaldehyde in the reaction solution is maintained 10 wt% or less.

5. A method of preparing 2-amino-5-methylthiazole comprising adding thiourea to an aqueous solution containing 2-chloropropionaldehyde and reacting the mixture at a temperature between 20 and 120°C.

6. A method of preparing 2-amino-5-methylthiazole

comprising adding thiourea to the aqueous solution containing 2-chloropropionaldehyde which is obtained by the method described in claim 3 or 4, and reacting the mixture at a temperature between 20 and 120°C.

INTERNATIONAL SEARCH REPORT

Inter   nal Application No
PCT/JP 99/05895

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C45/63 C07C47/14 C07D277/40

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 C07C 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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 484 742 A (KUREHA CHEMICAL IND CO LTD) 13 May 1992 (1992-05-13) cited in the application page 3; example 1 ---	1-6
Y	US 4 096 187 A (BONFIELD JOHN HENRY ET AL) 20 June 1978 (1978-06-20) claims --- -/--	1-6

☒ Further documents are listed in the continuation of box C.

☒ 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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"&" document member of the same patent family

Date of the actual completion of the international search 23 May 2000	Date of mailing of the international search report 06/06/2000
Name and mailing address of the ISA 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	Authorized officer Bonnevalle, E

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Inte onal Application No
PCT/JP 99/05895

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WAKASUGI T ET AL: "One-pot preparation of 2-(chloromethyl)dioxolanes and 2-aminothiazoles from (chloromethyl)trioxanes" CHEM. LETT. (CMLTAG,03667022);1994; (11); PP.2039-42, XP000541386 Nishiki-machi;Kureha Chem. Industry Co., Ltd., Nishiki Plant; Iwaki; 974; Japan (JP) cited in the application the whole document -----	1-6

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte   onal Application No
PCT/JP 99/05895

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