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(54) Title: PROCESS FOR THE PREPARATION OF 2-HYDROXY-4-METHYLTHIO BUTYRIC ACID ESTERS

(57) **Abstract:** An industrial process for the preparation of 2-hydroxy-4-methylthiobutyric acid esters comprising substantially monomers which process comprises reacting 2-hydroxy-4-methylthiobutyric acid, with an alcohol in the presence of an acid catalyst characterised in that the acid is the direct product of the hydrolysis of 2-hydroxy-4-methylthiobutyronitrile and the process is carried out in the presence of water and at a temperature of from 30 to 150 °C.

PROCESS FOR THE PREPARATION OF 2-HYDROXY-4-METHYLTHIO BUTYRIC ACID ESTERS

The present invention relates to an industrial process for the preparation of 2-hydroxy-4-methylthiobutyric acid esters.

2-Hydroxy-4-methylthiobutyric acid is known to be used as a methionine analogue for feeding breeding animals. This product is marketed under the trade names Rhodimet AT 88™ and Alimet™.

It is known to prepare the 2-hydroxy-4-methylthiobutyric acid by various processes by hydrolysing the 2-hydroxy-4-methylthiobutyronitrile. The hydrolysis can be carried out with an inorganic acid such as hydrochloric or sulphuric acid. Alternatively it can be carried out by enzymatic hydrolysis.

2-Hydroxy-4-methylthiobutyric acid esters are also used as a means of introducing methionine to animals, in particular to ruminants as disclosed in French application No. 98 14249. The acid is not stable because it is consumed by microorganisms present in the rumen of the animal and in many cases, the ester form is the favoured means of introducing the methionine into the bloodstream of the animal.

The ester may be prepared by esterification of the hydrochloride salt of the acid and then reacting it with the alcohol. Such processes are known from US Patents 3,850,987 and 3,761,518. It has also been found possible to prepare the 2-hydroxy-4-methylthiobutyric acid esters by a process which comprises hydrating 2-hydroxy-4-methylthiobutyronitrile with sulphuric acid and then esterifying the product obtained. Such processes are disclosed in US Patents No. 4524077and 4912257 and WO 96/40630.

It is known in the art that the monomers exhibit greater biological efficacy than the dimers and oligomers and it is therefore preferred to produce a product with minimum oligomers.. Thus, when producing the ester, it is preferable to reduce the amount of oligomers in the starting acid. To reduce the amount of dimers and oligomers in the acid, the acid may be purified by various means such as liquid/liquid extraction.

We have found that 2-hydroxy-4-methylthiobutyric acid esters containing a small amount of oligomers can be produced by the esterification of 2-hydroxy-4-methylthiobutyric acid without the need to pre-treat the acid before the esterification reaction when the esterification reaction is carried out under specific conditions. Furthermore, we have found that this process is particularly suitable for use as an industrial process.

Accordingly, the present invention provides an industrial process for the preparation of 2-hydroxy-4-methylthiobutyric acid esters comprising substantially monomers which process comprises reacting 2-hydroxy-4-methylthiobutyric acid, with an alcohol in the presence of an acid catalyst characterised in that the acid is the direct product of the hydrolysis of 2-hydroxy-4-methylthiobutyronitrile and the process is carried out in the presence of water and at a temperature of from 30 to 150°C.

It will of course be understood by the person skilled in the art that the 2-hydroxy-4-methylthiobutyric acid obtained as a direct product of the hydrolysis of 2-hydroxy-4-methylthiobutyronitrile from an industrial process comprises a mixture of monomers, dimers and higher oligomers.

The process of the present invention, thus, provides the advantage over the prior art by avoiding the purification of the acid prior to esterification. This is, of course, an important advantage in an industrial process, avoiding the use of additional large equipment.

In the process of the present invention 2-hydroxy-4-methylthiobutyric acid obtained directly from the hydration of 2-hydroxy-4-methylthiobutyronitrile is reacted with an alcohol. The acid is, thus, likely to be a direct product of an industrial process and will therefore be a mixture of monomers, dimers and other oligomers. The acid may also comprise impurities such as water, sulphuric acid and ammonium sulphate. In particular, the acid may be produced from an industrial process for the production of 2-hydroxy-4-methylthiobutyric acid and may be, for example, Rhodimet™ AT 88, sold by Rhône Poulenc.

The alcohol, suitable for use in the present process, may be an aliphatic alcohol containing 1 to 10 carbon atoms. The alcohol may be linear or branched. Preferably, the alcohol is branched, especially isopropyl alcohol. The use of isoproyl alcohol is particularly preferred as the 2-hydroxy-4-methylthiobutyric acid isopropyl ester has a high biological efficacy.

The acid and the alcohol is suitably reacted in a molar ratio of from 1 to 20. Where the process is operated as a continuous process, the overall molar ratio of acid to alcohol is preferably 1 to 10. The amount of alcohol in the continuous reaction may be maintained at the desired level by recycle. Where the process is operated as a batch process, the molar ratio of acid to alcohol is preferably from 2 to 10. Unreacted alcohol may be recycled.

The esterification process of the present invention is carried out in the presence of water. In particular, it has been found that the conversion of acid oligomers is particularly favoured when water is present at the beginning of the esterification reaction.

The esterification process is carried out in the presence of an acid catalyst. Catalysts suitable for use in the process include acids having a pK_a of less than 3, for example sulphuric acid and trifluoroacetic acid. Alternatively, an acid resin may be used to catalyse the process, especially a sulphonic acid resin, for example Amberlyst 15 as produced by Rohm & Haas.. The process may also be catalysed using alumina or an aluminosilicate, for example a zeolite or through the use of an enzyme.

The catalyst may be present in the reaction process in a concentration of suitably at least 0.01 mole of catalyst per mole of 2-hydroxy-4-methylthiobutyric acid, preferably from 0.02 to 0.2 mole of catalyst per mole of acid.

The process may be carried out under atmospheric or elevated pressure. Where the process is carried out under elevated pressure, the pressure may be any suitable pressure, for example up to 50 bar.

The process is carried at a temperature of from 30 to 150°C. Preferably, the process is carried out at a temperature of from 60 to 120°C, especially from 80 to 100°C.

The process may be carried out continuously, semi-continuously or batchwise. In particular for an industrial process, it is preferred to operate a continuous process.

As the esterification process is an equilibrium reaction, it is preferred to continuously remove water formed in the reaction in order to shift the reaction towards the ester products. The water formed in the reaction may be removed by any suitable means appropriate to an industrial process, for example by the distillation. In some cases, the alcohol may be added to form an azeotrope. Also possible, is the use of ternary distillation.

The resulting product stream comprises the ester, water, unreacted alcohol, unreacted acid, a small amount of acid oligomers and catalyst.

Where the catalyst used in the process is an acid, for example sulphuric acid, it is preferred at the end of the reaction to neutralise the acid. This step may be carried out by the addition of a base having a pK_a greater than 8, for example ammonia or ammonium hydroxide. Where the catalyst used in the process is a solid, such as a resin, it is preferred at the end of the reaction to remove the catalyst from the product stream by filtration. Additional solid by-products may also be separated and removed from the product stream by filtration.

The product stream is suitably treated to remove any unreacted alcohol. This treatment step may be carried out by any suitable method, for example by distillation. The alcohol may be recycled back to the reactor.

Finally, the treated product stream comprising the ester may be washed. The washing step is suitably carried out by the addition of water, optionally comprising an additive to enhance the decantation. Suitable additives include salts such as ammonium sulphate. The resulting mixture will separate into an organic phase and an aqueous phase. The organic phase may then be isolated and, if desired, washed at least one more time. The resulting organic phase may be distilled to separate the ester from the unwanted by-products. The unwanted by-products separated from the ester product may be recycled back to the reactor.

Alternatively, the product stream may be treated to isolate the ester product by liquid/liquid extraction or by simple distillation.

The resulting product stream comprises a high yield of monomeric ester, at least 55%, more typically at least 90%, especially at least 95%.

The present invention will now be illustrated with reference to the following examples:

Example 1: Synthesis of 2-hydroxy-4-methylthiobutyric acid isopropyl ester (MHBI) Using an Acid Catalyst

Step (a) Esterification:

170.7 g of Rhodimet AT88, containing 88% acid (68% monomers and 20% oligomers) and 12% water, and 180.3 g of isopropanol were loaded into a reactor. 19.6 g of 95% sulphuric acid was added whilst maintaining the temperature at reflux temperature. The acid was added in one aliquot. After the acid had been introduced into the reactor, the reaction was maintained at reflux temperature for two hours.

The temperature was increased to 90°C. Additional isopropanol (420g) was added continuously over 5 hours and the azeotrope of alcohol and water was removed continuously.

Step (b) Neutralisation/Removal of Water:

The reaction mixture was cooled to 40°C and then neutralised to pH 7/8 by the addition of 22 g of 32% weight ammonium hydroxide.

The resulting product was distilled at 60°C under a pressure of 50millibar for approximately 1 hour.

Step (c) Washing:

The distillate product was then washed by adding 95 g of 5% aqueous ammonium sulphate, with stirring. The resulting mixture was stirred at a temperature of 40°C for 15 minutes. The stirring was stopped and the mixture left to stand at 40°C for 30 minutes. The aqueous phase was then separated from the organic phase .

The organic phase was washed again with 30 g of water.

Step (d) Removal of Water/Isopropanol:

The organic phase was then distilled at 100°C under a pressure of 5mbar for approximately 2 hours to yield a product stream comprising mainly the ester.

The resulting product stream was analysed and was found to contain 92% monomeric ester, 5% dimer and 2.5% unreacted acid .

Example 2: Synthesis of 2-hydroxy-4-methylthiobutyric acid isopropyl ester (MHBI) Using a Resin Catalyst

179.6 g of Rhodimet AT88, containing 88% acid (68% monomers and 20% oligomers) and 12% water, and 179.6 g of isopropanol were loaded into a reactor. 30 g of Amberlyst 15 resin was introduced into the reactor whilst maintaining the temperature at reflux temperature. The reaction was maintained at this temperature for 5 hours.

Analysis of the resulting product showed a 65% conversion of acid (monomers and oligomers) with a yield of 60% monomeric ester and 5% dimeric ester.

This example shows the feasibility of using a resin catalyst.

Example 3: Esterification of the By-Product Stream

101 g of a distillation stream containing 40g dimeric ester, 16g monomeric acid and 6.5g dimeric acid; 224g of isopropanol and 17g of water were loaded into a reactor. 11.5 g of 95% sulphuric acid was added in one aliquot. After the acid had been introduced the reaction was maintained at reflux temperature for five hours.

The reaction was terminated and product stream analysed. It was found to contain 55g monomer ester, 17g monomer acid, 4g dimer ester and 3g dimer acid.

This example proves the feasibility of recycling a stream containing a substantial quantity of the ester dimers.

CLAIMS

1. An industrial process for the preparation of 2-hydroxy-4-methylthiobutyric acid esters comprising substantially monomers which process comprises reacting 2-hydroxy-4-methylthiobutyric acid, with an alcohol in the presence of an acid catalyst characterised in that the acid is the direct product of the hydrolysis of 2-hydroxy-4-methylthiobutyronitrile and the process is carried out in the presence of water and at a temperature of from 30 to 150°C .

2. A process as claimed in claim 1 in which the temperature is from 60 to 120°C.

3. A process as claimed in claim 2 in which the temperature is from 80 to 100°C.

4. A process as claimed in any one of the preceding claims in which the alcohol is a linear or branched aliphatic alcohol having 1 to 10 carbon atoms.

5. A process as claimed in claim 4 in which the alcohol is a branched alcohol.

6. A process as claimed in claim 5 in which the alcohol is isopropanol.

7. A process as claimed in any one of the preceding claims in which the molar ratio of acid to alcohol is from 1 to 10.

8. A process as claimed in any one of the preceding claims in which the acid catalyst is an acid having a pKa of less than 3, an acid resin, alumina or an aluminosilicate

9. A process as claimed in claim 8 in which the acid catalyst is sulphuric acid.

10. A process as claimed in claim 8 in which the acid catalyst is a resin catalyst.

11. A process as claimed in claim 9 in which any excess catalyst is separated from the ester product by the addition of a neutralising agent.

12. A process as claimed in claim 11 in which the neutralising agent is ammonium hydroxide.

13. A process as claimed in claim 10 in which any excess catalyst is separated from the ester product by filtration.

14. A process in which water is continuously withdrawn from the reaction.

15. A process as claimed in any one of the preceding claims in which any by-products are separated from the ester product by a treatment process comprising

(a) a first step of distilling the product stream to remove water,

(b) a second step of washing the product stream from step (a) to provide an organic phase and an aqueous phase, and

(c) a third step of distilling the organic phase to yield the ester product.

16. A process as claimed in any one of claims 1 to 14 in which any by-products are separated from the ester product by liquid/liquid extraction.

17. A process as claimed in any one of claims 1 to 14 in which any by-products are separated from the ester product by distillation

18. A process as claimed in any one of claims 15 to 17 in which the by-products are recycled to the reactor.

19. A process as claimed in any one of the preceding claims operated as a continuous process.

20. A process as claimed in any one of claims 1 to 18 operated as a batch process.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/01324

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C323/52 C07C319/20

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

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)

CHEM ABS Data, PAJ, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	US 4 000 318 A (K.A. FERGUSON ET AL) 28 December 1976 (1976-12-28) column 4, line 57 - column 5, line 12	1-4,8, 17,20
A	US 3 761 518 A (F.R. HAGLID) 25 September 1973 (1973-09-25) cited in the application column 5, lines 8-17	1-4,8, 17,20

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

☒ Patent family members are listed in annex.

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

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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 Van Amsterdam, L

INTERNATIONAL SEARCH REPORT

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