

PREPARATION METHOD FOR BETAININE MERCAPTOSUCCINATE (1:1)

CROSS-REFERENCE TO RELATED APPLICATION

5 The present disclosure claims the priority to and the benefit of Chinese Patent Application No. 202410639054.6 filed on 21 May 2024, the content of which is incorporated herein by reference in its entirety.

TECHNICAL FIELD

10 The present disclosure relates to a method for preparing a complex salt of betaine, and more specifically relates to a preparation method for betaine mercaptosuccinate (1:1).

BACKGROUND

15 In recent years, betaine can provide an active methyl group and participate in a methylation reaction in the metabolism of a bioorganism, leading to its increasingly wide applications in the livestock and poultry industry as well as the feed industry, with new applications being continuously developed. Due to the strong hygroscopicity, betaine is prone to moisture absorption during transport and storage, thus adversely affecting its application quality. Complex salts of betaine have attracted increasing
20 attention. However, a salt formation process of betaine usually requires the use of an alcohol-based solvent or involves a relatively complicated separation process.

GB1240313 discloses a preparation method for betaine thiomalate, wherein a methanol solution of betaine and a methanol solution of thiomalic acid are used as raw materials to react and generate betaine thiomalate. This method not only requires a
25 multi-step separation and purification process, but also achieves a yield of only 68%.

GB987849 discloses a preparation method for betaine fumarate. The inventor still holds that a good salt-formation result can only be obtained by reacting fumaric acid with betaine in an inert solvent, such as an alcohol-based solvent. However, the use of the alcohol-based solvent increases the environmental burden.

30 CN110724048 discloses a preparation method for betaine malate. To simplify the separation and purification procedures, the method improves the selectivity of the reaction by introducing the formation of a complex. This method increases the yield, but further raises the complexity of the reaction process and equipment, and increases the process costs.

35 In recent years, betaine mercaptosuccinate (1:1) has attracted extensive attention due to its unique properties. Betaine mercaptosuccinate features good stability and high-water solubility, thereby not only greatly reducing the hygroscopicity of betaine, but also retaining an inherent function of mercaptosuccinic acid itself, which is conducive to the development of more biochemical functions of this product.

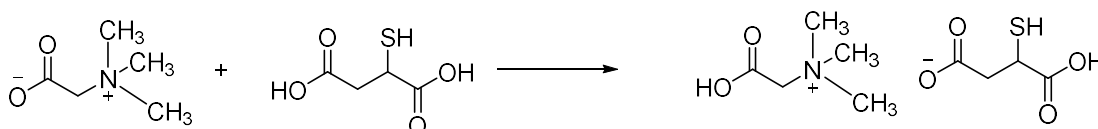
40 In view of the above, the present disclosure provides a preparation method for betaine mercaptosuccinate (1:1), which simplifies device requirements and operational procedures and meanwhile ensures the yield, and the product maintains a favorable stoichiometric ratio of 1:1. In addition, all raw materials used in each step of this method are commercially available with moderate cost and sufficient supply, thereby

providing the feasibility for large-scale industrial production of the product.

SUMMARY

An objective of the present disclosure is to provide a preparation method for betaine mercaptosuccinate (1:1), which features mild reaction conditions, simple process and device, easy operations, and environmental friendliness.

The present disclosure provides a preparation method for betaine mercaptosuccinate (1:1) represented by formula (I), comprising the following steps:



formula (I)

a) providing a mixture of mercaptosuccinic acid and water, wherein a weight ratio of mercaptosuccinic acid to water is from 1:2 to 1:8;

b) adding betaine, so that betaine directly reacts with mercaptosuccinic acid, wherein a molar ratio of mercaptosuccinic acid to betaine is from 1:1 to 1:1.1; and

c) crystallizing the product obtained in step b) to afford the betaine mercaptosuccinate (1:1) represented by formula (I).

In an embodiment, the molar ratio of mercaptosuccinic acid to betaine may be from 1:1 to 1:1.05, for example, 1:1, 1:1.03 or 1:1.05.

In an embodiment, the weight ratio of mercaptosuccinic acid to water may be from 1:2 to 1:5, preferably from 1:3 to 1:5, for example, 1:3, 1:4 or 1:5.

In an embodiment, in step a), the mixture of mercaptosuccinic acid and water is maintained at a first temperature, and the first temperature may be from 45°C to 75°C.

In an embodiment, in step b), betaine may directly react with mercaptosuccinic acid at a second temperature, and the second temperature may be from 45°C to 75°C.

In an embodiment, the first temperature and the second temperature may be the same, and may be from 45°C to 65°C, for example, 45°C, 50°C, 55°C, 60°C or 65°C.

Alternatively, the first temperature may be different from the second temperature, and the second temperature may be from 45°C to 65°C, for example, 45°C, 50°C, 55°C, 60°C or 65°C.

In an embodiment, a direct reaction time between betaine and mercaptosuccinic acid may be from 6 h to 10 h, for example, 6 h, 7 h, 8 h, 9 h or 10 h.

In an embodiment, the step c) may further comprise adding an organic solvent, allowing the resulting mixture to stand at room temperature until no more crystals are precipitated, collecting the resulting solid, pulverizing the solid, and then performing vacuum drying to obtain the betaine mercaptosuccinate (1:1) represented by formula (I).

In an embodiment, the organic solvent may comprise one or more of acetone, ethanol and isopropanol.

In an embodiment, a weight ratio of the organic solvent to mercaptosuccinic acid may be from 1:0.9 to 1:1.1, preferably 1:1.

The preparation method provided in the present disclosure has at least one of the following advantages:

1. the preparation method improves the selectivity of the reaction, increases the utilization rate of the raw materials, and greatly enhances the purity of betaine mercaptosuccinate (1:1);

2. all raw materials used in each step are commercially available, with wide sources and sufficient supply;

3. the preparation method features relatively mild reaction conditions, simple process, and easily controllable conventional operations in each reaction step, thereby reducing the process costs, and additionally, the formation of an intermediate complex is avoided due to the adoption of a mercapto substituent, compared to hydroxysuccinic acid, thereby further simplifying the process; and

4. the preparation method is environmentally friendly with reduced pollution, thus achieving green production.

DETAILED DESCRIPTION

Hereinafter, the present disclosure will be further illustrated in detail with reference to specific embodiments. However, the specific embodiments are provided merely for illustrative purposes, and are not intended to limit the present disclosure to the disclosed specific embodiments. A person skilled in the art will appreciate that specific features in any one of the following embodiments may be applied for any other embodiments without departing from the spirit of the present disclosure.

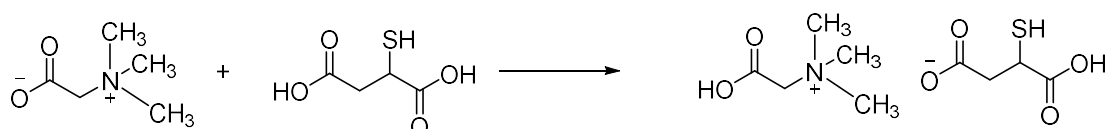
Hereinafter, unless otherwise defined, all terms used herein, including technical and scientific terms, shall have the same meanings as commonly understood by a person of ordinary skill in the art to which the present disclosure belongs. Terms, such as those defined in commonly used dictionaries, shall be construed as having meanings consistent with their contextual meanings in the relevant technical field, and shall not be interpreted in an idealized or overly formal sense unless expressly so defined herein.

As used herein, the term "direct reaction" or "directly react" refers to a reaction carried out without adding other reagents or reactants to form an intermediate product.

As used herein, the term "about" includes a stated value, and means within an acceptable deviation range of the stated value, as determined by a person of ordinary skill in the art in consideration of a relevant measurement and an error associated with the measurement of such quantity (i.e., limitations of the measurement system). For example, the term "about" may mean within one or more than one standard deviations, or within $\pm 20\%$, $\pm 10\%$ or $\pm 5\%$ of the stated value.

The "room temperature" herein specifically refers to a temperature range of 22°C - 25°C , and generally refers to 25°C .

The present disclosure provides a preparation method for betaine mercaptosuccinate (1:1) represented by formula (I), comprising the following steps:



formula (I)

a) providing a mixture of mercaptosuccinic acid and water, wherein a weight ratio of mercaptosuccinic acid to water is from 1:2 to 1:8;

5 b) adding betaine, so that betaine directly reacts with mercaptosuccinic acid, wherein a molar ratio of mercaptosuccinic acid to betaine is from 1:1 to 1:1.1; and

c) crystallizing the product obtained in step b) to afford the betaine mercaptosuccinate (1:1) represented by formula (I).

10 In an embodiment, in step a), the mixture of mercaptosuccinic acid and water is maintained at a first temperature, and the first temperature may be from 45°C to 75°C.

In an embodiment, in step a), mercaptosuccinic acid and water may be charged into a reactor, and rapidly heated to the first temperature under stirring. The reactor is not particularly limited, and any reactor capable of carrying out the above reaction may be used.

15 In an embodiment, the weight ratio of mercaptosuccinic acid to water may be from about 1:2 to about 1:8, preferably from about 1:2 to about 1:5, more preferably from about 1:3 to about 1:5. In a specific embodiment, the weight ratio of mercaptosuccinic acid to water may be 1:3, 1:4 or 1:5. In one embodiment, the weight ratio of mercaptosuccinic acid to water may be 1:3. In another embodiment, the weight ratio of mercaptosuccinic acid to water may be 1:4. In still another embodiment, the weight ratio of mercaptosuccinic acid to water may be 1:5. However, a person skilled in the art shall understand that the weight ratio of mercaptosuccinic acid to water in the embodiments of the present disclosure is not limited to the above values, and may be any value within the range of about 1:2 to about 1:8, for example, 1:3.5 or 1:2.6.

25 In an embodiment, in step b), betaine may directly react with mercaptosuccinic acid at a second temperature, and the second temperature may be from 45°C to 75°C.

In an embodiment, in step b), betaine may be added portionwise under stirring, so that betaine directly reacts with mercaptosuccinic acid at the second temperature. Herein, the direct reaction between betaine and mercaptosuccinic acid at the second temperature means that betaine reacts with mercaptosuccinic acid without adding other reagents or reactants to form other intermediates. For example, betaine reacts with mercaptosuccinic acid without adding other protecting agents to form other protected intermediates, or betaine reacts with mercaptosuccinic acid without adding other reagents to form other complex intermediates.

35 In an embodiment, the molar ratio of mercaptosuccinic acid to betaine may be from about 1:1 to about 1:1.1, preferably from about 1:1 to about 1:1.05, more preferably from about 1:1.03 to about 1:1.05. In a specific embodiment, the molar ratio of mercaptosuccinic acid to betaine may be 1:1, 1:1.01, 1:1.02, 1:1.03, 1:1.04 or 1:1.05. In one embodiment, the molar ratio of mercaptosuccinic acid to betaine may be 1:1. In another embodiment, the molar ratio of mercaptosuccinic acid to betaine may be 1:1.03. In still another embodiment, the molar ratio of mercaptosuccinic acid to betaine may

be 1:1.05. However, a person skilled in the art shall understand that the molar ratio of mercaptosuccinic acid to betaine in the embodiments of the present disclosure is not limited to the above values, and may be any values within the range of about 1:1 to about 1:1.1.

5 In an embodiment, the first temperature and the second temperature may each be from about 45°C to about 65°C, for example, 45°C, 50°C, 55°C, 60°C or 65°C. In a specific embodiment, the first temperature and the second temperature may be the same or different. In other words, the first temperature and the second temperature may be slightly different, but the reaction is preferably carried out at the same temperature. In
10 one embodiment, the first temperature and the second temperature may each be 45°C. In another embodiment, the first temperature and the second temperature may each be 55°C. In still another embodiment, the first temperature and the second temperature may each be 65°C. However, a person skilled in the art shall understand that the first temperature and the second temperature in the embodiments of the present disclosure
15 are not limited to the above values, and may each be any values within the range of about 45°C to about 65°C, for example, 45.5°C or 45.7°C.

In an embodiment, the reaction time in step b) may be from about 6 h to about 10 h. In a specific embodiment, the reaction time in step b) may be 6 h, 7 h, 8 h, 9 h or 10 h. However, a person skilled in the art shall understand that the reaction time in step
20 b) in the embodiments of the present disclosure is not limited to the above values, and may be any values within the range of about 6 h to about 10 h, for example, 6.5 h, 7.5 h or 8.5 h.

In an embodiment, the step c) may further comprise steps of adding an organic solvent, allowing the resulting mixture to stand at room temperature until no more
25 crystals are precipitated, collecting the resulting solid, pulverizing the solid, and then performing vacuum drying to obtain the betaine mercaptosuccinate (1:1) represented by formula (I). In a specific embodiment, the organic solvent may comprise one or more of acetone, ethanol and isopropanol. In one embodiment, the organic solvent may be any one of acetone, ethanol and isopropanol. In addition, a weight ratio of the
30 organic solvent to mercaptosuccinic acid may be from about 1:0.9 to about 1:1.1, preferably 1:1. However, a person skilled in the art shall understand that the crystallization method in step c) is not limited to the specifically disclosed methods described above.

35 **EXAMPLES**

Example 1

Mercaptosuccinic acid (150 g, 1.0 mol) and water (750 g) were charged into a reactor, stirred uniformly, and then rapidly heated to 45°C. Betaine (122.8 g, approximately 1.05 mol) was added portionwise under stirring. After the addition was
40 completed, the mixture was continuously stirred and reacted for 10 hours. Upon completion of the reaction, the mixture was cooled to room temperature, and filtered to remove insoluble substances. The filtrate was concentrated to remove most of the solvent, followed by the addition of followed by the addition of acetone (150 g), and the mixture was allowed to stand at room temperature until no more crystals were

precipitated (a small amount of seed crystals may be added to accelerate the crystallization process). The resulting solid was collected, pulverized, and then vacuum-dried to afford 245.7 g of betaine mercaptosuccinate (1:1) as a white solid with a yield of approximately 92.0%.

5 The product was confirmed to be consistent with the standard sample by ion chromatography comparison.

Example 2

10 Mercaptosuccinic acid (150 g, 1.0 mol) and water (450 g) were charged into a reactor, stirred uniformly, and then rapidly heated to 60°C. Betaine (117 g, 1.0 mol) was added portionwise under stirring. After the addition was completed, the mixture was continuously stirred and reacted for 6 h. Upon completion of the reaction, the mixture was cooled to room temperature, and filtered to remove insoluble substances. The filtrate was concentrated to remove most of the solvent, followed by the addition of ethanol (150 g), and the mixture was allowed to stand at room temperature until no more crystals were precipitated (a small amount of seed crystals may be added to accelerate the crystallization process). The resulting solid was collected, pulverized, and then vacuum-dried to afford 225.3 g of betaine mercaptosuccinate (1:1) as a white solid with a yield of approximately 84.4%.

15 The product was confirmed to be consistent with the standard sample by ion chromatography comparison.

Example 3

20 Mercaptosuccinic acid (150 g, 1.0 mol) and water (600 g) were charged into a reactor, stirred uniformly, and then rapidly heated to 55°C. Betaine (120.5 g, approximately 1.03 mol) was added portionwise under stirring. After the addition was completed, the mixture was continuously stirred and reacted for 8 h. Upon completion of the reaction, the mixture was cooled to room temperature, and filtered to remove insoluble substances. The filtrate was concentrated to remove most of the solvent, followed by the addition of acetone (150 g), and the mixture was allowed to stand at room temperature until no more crystals were precipitated (a small amount of seed crystals may be added to accelerate the crystallization process). The resulting solid was collected, pulverized, and then vacuum-dried to afford 236.5 g of betaine mercaptosuccinate (1:1) as a white solid with a yield of approximately 88.6%.

25 The product was confirmed to be consistent with the standard sample by ion chromatography comparison.

Example 4

30 Mercaptosuccinic acid (150 g, 1.0 mol) and water (600 g) were charged into a reactor, stirred uniformly, and then rapidly heated to 55°C. Betaine (122.8 g, approximately 1.05 mol) was added portionwise under stirring. After the addition was completed, the mixture was continuously stirred and reacted for 8 h. Upon completion of the reaction, the mixture was cooled to room temperature, and filtered to remove insoluble substances. The filtrate was concentrated to remove most of the solvent, followed by the addition of isopropanol (150 g), and the mixture was allowed to stand at room temperature until no more crystals were precipitated (a small amount of seed crystals may be added to accelerate the crystallization process). The resulting solid was

collected, pulverized, and then vacuum-dried to afford 232.9 g of betaine mercaptosuccinate (1:1) as a white solid with a yield of approximately 87.2%.

The product was confirmed to be consistent with the standard sample by ion chromatography comparison.

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Example 5

Mercaptosuccinic acid (150 g, 1.0 mol) and water (600 g) were charged into a reactor, stirred uniformly, and then rapidly heated to 65°C. Betaine (117 g, 1.0 mol) was added portionwise under stirring. After the addition was completed, the mixture was continuously stirred and reacted for 10 h. Upon completion of the reaction, the mixture was cooled to room temperature, and filtered to remove insoluble substances. The filtrate was concentrated to remove most of the solvent, followed by the addition of isopropanol (150 g), and the mixture was allowed to stand at room temperature until no more crystals were precipitated (a small amount of seed crystals may be added to accelerate the crystallization process). The resulting solid was collected, pulverized, and then vacuum-dried to afford 231.2 g of betaine mercaptosuccinate (1:1) as a white solid with a yield of approximately 86.6%.

The product was confirmed to be consistent with the standard sample by ion chromatography comparison.

Comparative Example 1

Mercaptosuccinic acid (150 g, 1.0 mol) and methanol (600 g) were charged into a reactor, stirred uniformly, and then rapidly heated to 55°C. A methanol solution of betaine (comprising 117 g, 1.0 mol of betaine and 400 g of methanol) was added portionwise under stirring. After the addition was completed, the mixture was continuously stirred and reacted under reflux for 6 h. Upon completion of the reaction, the mixture was cooled to room temperature, and allowed to stand until no more crystals were precipitated (a small amount of seed crystals may be added to accelerate the crystallization process). The resulting solid was collected, pulverized, and then vacuum-dried to afford 165.5 g of betaine mercaptosuccinate (1:1) as a white solid with a yield of approximately 62.0%.

The product was confirmed to be consistent with the standard sample by ion chromatography comparison.

Comparative Example 2

Mercaptosuccinic acid (150 g, 1.0 mol) and methanol (500 g) were charged into a reactor, stirred uniformly, and then rapidly heated to 55°C. A methanol solution of betaine (comprising 117 g, 1.0 mol of betaine and 350 g of methanol) was added portionwise under stirring. After the addition was completed, the mixture was continuously stirred and reacted under reflux for 4 h. Upon completion of the reaction, the mixture was cooled to room temperature, and allowed to stand until no more crystals were precipitated (a small amount of seed crystals may be added to accelerate the crystallization process). The resulting solid was collected, pulverized, and then vacuum-dried to afford 151.3 g of betaine mercaptosuccinate (1:1) as a white solid with a yield of approximately 56.7%.

The product was confirmed to be consistent with the standard sample by ion chromatography comparison.

Relevant details of the above experiments were summarized in Table 1 below.
Table 1. Examples and relevant data of the Examples.

No.	Raw materials	Molar ratio of mercaptosuccinic acid to betaine	Temperature (°C)	Reaction time (h)	Yield
Example 1	Mercaptosuccinic acid/water+betaine	1:1.05	45	10	92.0%
Example 2	Mercaptosuccinic acid/water+betaine	1:1	60	6	84.4%
Example 3	Mercaptosuccinic acid/water+betaine	1:1.03	55	8	88.6%
Example 4	Mercaptosuccinic acid/water+betaine	1:1.05	55	8	87.2%
Example 5	Mercaptosuccinic acid/water+betaine	1:1	65	10	86.6%
Comparative Example 1	Mercaptosuccinic acid/methanol+betaine/methanol	1:1	55	6	62.0%
Comparative Example 2	Mercaptosuccinic acid/methanol+betaine/methanol	1:1	55	4	56.7%

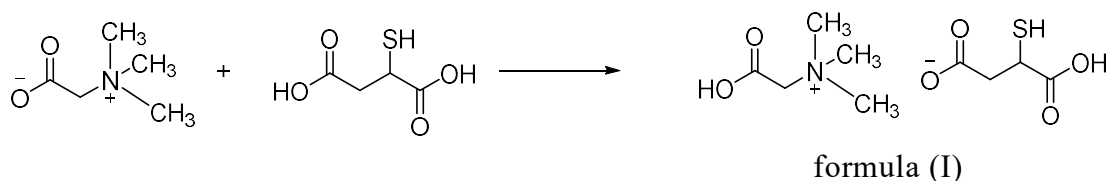
Comparative Example 1 and Comparative Example 2 adopted the conventional preparation method in the art, which is similar to the method disclosed in GB1240313 as mentioned in the background art. Alcohol-based solvents commonly used in the art were used for the salt-formation reaction of betaine. However, compared to the method disclosed in GB1240313, the preparation method adopted in Comparative Examples 1 and 2 appropriately extended the reaction time from 1 h to 4 h or 6 h, so that the reaction time in the Comparative Examples is equivalent to that in the Examples. By comparison, under the conditions of the same molar ratio of mercaptosuccinic acid to betaine, a similar reaction temperature and equivalent reaction time, the preparation method in the Examples can achieve a significantly improved yield.

In addition, in the present disclosure, an aqueous solution of mercaptosuccinic acid directly reacts with betaine, thereby omitting the step of generating intermediate complexes, obtaining the desired product more directly and efficiently, simplifying the preparation process and avoiding impurities potentially introduced by intermediates.

Although the present disclosure has been described with reference to specific embodiments, some modifications and equivalents will be apparent to a person skilled in the art, and are intended to be encompassed within the scope of the present disclosure.

WHAT IS CLAIMED IS:

1. A preparation method for betaine mercaptosuccinate (1:1) represented by formula (I), comprising:



a) providing a mixture of mercaptosuccinic acid and water, wherein a weight ratio of mercaptosuccinic acid to water is from 1:2 to 1:8;

b) adding betaine, so that betaine directly reacts with mercaptosuccinic acid, wherein a molar ratio of mercaptosuccinic acid to betaine is from 1:1 to 1:1.1; and

c) crystallizing the product obtained in step b) to afford betaine mercaptosuccinate (1:1) represented by formula (I).

2. The preparation method according to claim 1, wherein the molar ratio of mercaptosuccinic acid to betaine is from 1:1 to 1:1.05, for example, 1:1, 1:1.03 or 1:1.05.

3. The preparation method according to claim 1 or 2, wherein the weight ratio of mercaptosuccinic acid to water is from 1:2 to 1:5, preferably from 1:3 to 1:5, for example, 1:3, 1:4 or 1:5.

4. The preparation method according to claim 1 or 2, wherein
in step a), the mixture of mercaptosuccinic acid and water is maintained at a first temperature, and the first temperature is from 45°C to 75°C, and
in step b), betaine directly reacts with mercaptosuccinic acid at a second temperature, and the second temperature is from 45°C to 75°C.

5. The preparation method according to claim 4, wherein the first temperature and the second temperature are the same, and both are from 45°C to 65°C, for example, 45°C, 50°C, 55°C, 60°C or 65°C.

6. The preparation method according to claim 4, wherein the first temperature is different from the second temperature, and the second temperature is from 45°C to 65°C, for example, 45°C, 50°C, 55°C, 60°C or 65°C.

7. The preparation method according to claim 1 or 2, wherein a direct reaction time between betaine and mercaptosuccinic acid is from 6 h to 10 h, for example, 6 h, 7 h, 8 h, 9 h or 10 h.

8. The preparation method according to claim 1 or 2, wherein step c) further comprises adding an organic solvent, allowing the resulting mixture to stand at room

temperature until no more crystals are precipitated, collecting the resulting solid, pulverizing the solid, and then performing vacuum drying to afford betaine mercaptosuccinate (1:1) represented by formula (I).

9. The preparation method according to claim 8, wherein the organic solvent comprises one or more of acetone, ethanol and isopropanol.

10. The preparation method according to claim 8, wherein a weight ratio of the organic solvent to mercaptosuccinic acid is from 1:0.9 to 1:1.1, preferably 1:1.