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(54) Title: PROCESS FOR THE PREPARATION OF SUCRALOSE BY THE CHLORINATION OF SUGAR WITH TRIPHOSGENE (BTC)

(57) Abrégé/Abstract:
In one embodiment of the invention a method to prepare sucralose-6-acylate through chlorinating sucrose-6-acylater by BTC in the process of sucralose preparation is disclosed. In this embnodiment a Vilsmeier reagent is firstly prepared belowe 0 °C by dissolving BTC in DMF or in component solvent, containing DMF, toluene, dichloroethane, chloroform and carbon tetrachloride. Consequently, sucrose-6-ester was chlorinated by Vilsmeier reagent. BTC can also be dissolved in one or several organic solvent such as toluene, dichloroethane, chloroform and carbon tetrachloride, and added to a DMF solution of sucrose-6-acylate for chlorination. Sucralose was prepared through de-esterifying the obtained sucralosed 6-ester using sodium methoxide/methanol or sodium ethoxide/ethanol.

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PROCESS FOR THE PREPARATION OF SUCRALOSE BY THE CHLORINATION OF SUGAR WITH TRIPHOSGENE (BTC)

CROSS-REFERENCE TO RELATED APPLICATION

[0001] The present application claims priority to U.S. Patent Application No. 11/552,789 filed on October 25, 2006, the disclosure of which is hereby incorporated by reference as if fully set forth herein.

FIELD OF THE INVENTION

[0002] The present invention relates to a method of making sucralose.

BACKGROUND OF THE INVENTION

[0003] The monoester method has been used in the synthesis of sucralose. Converted to sucrose-6-ester from sucrose, sucralose-6-ester is generated through chlorinating sucrose-6-ester. Sucralose is prepared through alcoholysis of sucralose-6-ester by using sodium methoxide/methanol or sodium ehtoxide/ethanol. The commonly used chlorinating reagent is a Vilsmeier reagent, which was usually prepared through reacting DMF with phosgene or with thionyl chloride. A major drawback of such methods is the amount of sulfur dioxide emitted through chlorination which leads to increase treatment procedures and requirements for equipment. Further because phosgene is a strongly toxic gas, it is not suitable to store, transport and use.

[0004] Accordingly there is a need in the art for an inproved method making sucralose at high yield with less toxic by products.

SUMMARY OF THE INVENTION

[0005] In one embodiment fo the present invention a method for the preparation of a sucralose from sucrose-6-ester is provided comprising using BTC to generate a Vilsmeier reagent for chlorination wherein the Vilsmeier reagent is genreated by dissolving BTC in DMF and wherein the mole equivalents of BTC:sucrose-6-ester is in the range of about 2.8:1 to 3.5:1.

DETAILED DESCRIPTION

[0006] The following description of the invention is intended to illustrate various embodiments of the invention. As such, the specific modifications discussed are not to be construed as limitations on the scope of the invention. It will be apparent to one skilled in the art that various equivalents, changes, and modifications may be made without departing from the scope of the invention, and it is understood that such equivalent embodiments are to be included herein.

[0007] In one embodiment of the present invention a method for the chlorination of sugars to produce chlorodeoxy derivatives, and in particular to the chlorination of sugars and sugar derivatives in the preparation of chlorodeoxy sugar sweeteners such as sucralose (4,1',6'-trichloro-4,1',6'-trideoxygalactosucrose) is provided.

[0008] In one aspect of the invention, a Vilsmeier reagent is prepared by adding a chlorination reagent to a solvent comprising DMF or DMF and one or a mixture of other organic solvent such as toluene, cyclohexane, dichloroethane, chloroform and carbon tetrachloride. Sucrose-6-ester is dissolved into solvent. Both the Vilsmeier reagent and the DMF solution of sucrose-6-ester are chilled to below 0 °C before

mixing. The Vilsmeier reagent is then added to DMF solution of sucroses-6-ester dropwise so that the reaction temperature is kept below 5 °C. The reaction mixture is stirred at a temperature below 5 °C for 2 h after the addition of Vilsmeier reagent is complete. The reaction mixture is then warmed up at room temperature and maintained at room temperature for another 2 h. The reaction is then heated for 2-3 h to reach 110 °C and refluxed at 110 °C for 3 h. Afterwards, the reaction mixture is cooled to room temperature naturally. The pH of the reaction mixture is first adjusted to 8-9 by ammonia hydroxide/methanol solution (1:1), and then to 6-7 by glacial acetic acid. After removing most of the solvent by distillation under reduced pressure, the sucrose-6-ester is extracted by ethyl acetate and water. The combined organic phase is distilled under reduced pressure to afford sucralose-6-ester syrup. The sucralose-6-ester is then converted to sucralose by de-esterification using sodium methoxide/methanol or sodium ethoxide/ethanol.

[0009] In another aspect of the invention, a chlorination reagent can also be dissolved in one or several organic solvents, such as toluene, cyclohexane, dichloroethane, chlooform and carbon tetrachloride, before it is added into the DMF solution of sucrose-6-acetate with the same protocol as described above.

[0010] The chlorination reagent can be selected from a group consisting of triphenylhydrazine, phosphoric chloride, thionyl chloride, phosgene, oxalyl chloride. It is preferably triphosgene (Bis(trichloromethyl) carbonate, BTC). BTC is safe and convenient to use, and it causes no pollution and corrosion concerns.

[0011] The concentration of the sucrose-6-ester is preferably from 0.1 to 0.11 mol/L.

[0012] The mole equivalent (ME) of chlorination reagent comparing to sucrose-6-ester is from 2.8 to 3.5.

[0013] The reaction can be carried out under vacuum to avoid the oxidation of the reaction mixture by oxygen in ambient atmosphere. Alternitavley undesired oxidation may be avoided by refluxing the reaction mixture in the presence of a low-boiling-point organic solvent such as cyclohexane, dichloroethane, ethyl acetate, chloroform and carbon tetrachloride.

[0014] **EXAMPLES**

[0015] **Example 1: Chlorination of Sucrose-6-ester with BTC dissolved in DMF**

[0016] Sucrose-6-acetate (30 g, 0.08 mol) was dissolved in DMF (300 mL) and maintained at a temperature below 0 °C. BTC (80 g, 0.27 mol) was gently added to DMF (500 mL) at a temperature below 0 °C to prepare the Vilsmeier reagent. The Vilsmeier reagent was added to the DMF solution of sucrose 6-acetate slowly to keep the reaction temperature below 5 °C. The reaction was stirred at a temperature below 5 °C for 2 h and another 2 h at ambient temperature. The reaction mixture was then was heated to 110 °C slowly and refluxed at 110 ºC for 3 h. After the reaction was completed, the reaction mixture was allowed to cool to ambient temperature naturally. The reaction mixture was neutralized with ammonia hydroxide/methanol (1:1, 400 mL) to reach pH 8-9. After the reaction mixture was stirred for 5 min at ambient

temperature, the pH of the reaction was further adjusted to 6-7 by adding glacial acetic acid. Then most of the solvent was removed by distillation under reducing pressure. Distilled water (100 mL) and ethyl acetate (500 mL) were added to the remaining solution. The mixture was stirred for 1 h at ambient temperatre and filtered. The filter cake was washed with ethyl acetate (150 mL). The water phase of the filtrate was extracted with ethyl acetate (3x200 mL). The combined organic phase was washed with brine (2x100 mL) and then concentrated to around 400 mL by distillation under reduced pressure at a temperature below 60 °C. The remaining solution was decolored by activated charcoal (10 g), filtered and concentrated into syrup (40 g, containing 20 g (0.045 mol) sucralose 6-acetate, yield is 56%).

[0017] Example 2: Chlorination of Sucrose-6-ester with BTC dissolved in Toluene

[0018] The reaction was carried out following the same protocol as example 1 except that a toluene solution of BTC was added directly to the DMF solution of sucrose-6-acetate (30 g, 0.08 mol) to initiate the chlorination reaction. The toluene solution of BTC was prepared by dissolving BTC (80 g, 0.27 mol) in cooled toluene (400 mL) below 0 °C. The product was a syrup containing 22 g sucralose 6-acetate (0.05 mol) with a yield of 62.5%.

[0019] Example 3: Preparation of Sucralose from Sucralose-6-acetate

[0020] Twenty percent sodium methoxide/methanol (4 g, 0.015 mol NaOMe) solution was added to a 15 °C methanol (100 mL) solution of Sucralose 6-acetate (10 g, 0.023 mol). The mixture was stirred for 5 h at room temperature. The reaction was

neutralized and filtered through hydrogen strong acidic ion exchange resin, which was cleansed by methanol. The filtrate was concentrated under reduced pressure below 30 °C, to a soft foam. The foam was dissolved in distilled water (100 mL), and the solution was extracted by ethyl acetate (50 mL). The aqueous phase was then decolored with activated charcoal (0.5 g), filtered to remove the activated charcoa and washed with distilled water (2x300 mL). The filtrate was concentrated to syrup by distillation under reduced pressure at room temperature. Distilled water (8 mL) was added to dissolve the syrup at 80 ºC. After the solution was cooled to below 20 °C, crystal seeds were added to the solution. The formed crystals were filtered and washed by small amount of cold water, dried, then dried in crystallizing dish under reduced pressure at 45-50 °C to produce sucralose (5 g, 0.013 mol, yield 86%).

[0021] As stated above, the foregoing is merely intended to illustrate various embodiments of the present invention. The specific modifications discussed above are not to be construed as limitations on the scope of the invention. It will be apparent to one skilled in the art that various equivalents, changes, and modifications may be made without departing from the scope of the invention, and it is understood that such equivalent embodiments are to be included herein. All references cited herein are incorporated by reference as if fully set forth herein.

AMENDED CLAIMS

received by the International Bureau on 15 July 2008 (15.07.2008).

1. A method for the preparation of sucralose, comprising a step of chlorinating sucrose-6-ester using a chlorination composition comprising BTC.

2. The method of claim 1, wherein the chlorination composition comprises at least one organic solvent.

3. The method of claim 1, wherein the chlorination composition comprises at least one of DMF, cyclohexane, toluene, dichlothane, chloroform, carbon tetrachloride, ethyl acetate, and a combination thereof.

4. The method of claim 1, wherein the chlorination composition comprises a Vilsmeier reagent.

5. The method of claim 4, wherein the Vilsmeier reagent is prepared by dissolving BTC in a DMF composition, and wherein the DMF composition comprises DMF and optionally, one or more organic solvents.

6. The method of claim 1, wherein the step of chlorinating sucrose-6-ester using a chlorination composition comprises:

dissolving BTC in one or more organic solvents; and

adding the BTC solution into a DMF solution of sucrose-6-ester.

7. The method of claim 6, wherein the organic solvent is selected from a group consisting of DMF, cyclohexane, toluene, dichlothane, chloroform, carbon tetrachloride, and ethyl acetate.

8. The method of claim 1, wherein the mole equivalents of BTC:sucrose-6-ester is in the range of about 2.8:1 to about 3.5:1.

9. The method of claim 1, wherein the chlorination step proceeds at a normal pressure or a reduced pressure.

10. The method of claim 1, further comprising:

cooling the chlorination composition to a temperature of below about 0 °C before contacting the chlorination composition with the sucrose-6-ester;

maintaining the temperature at under about 5°C as the chlorination composition is contacted with sucrose-6-ester to form a first mixture; and

warming the first mixture to room temperature.

11. The method of claim 10, further comprising:

maintaining the first mixture at room temperature for about 3 hours to form a second mixture;

heating the second mixture to about 110°C; and

maintaining the second mixture at a temperature of about 110°C for about 3 hours.

12. A method for the preparation of sucralose, comprising a step of chlorinating sucrose-6-ester using a Vilsmeier reagent, wherein the Vilsmeier reagent is generated by dissolving BTC in DMF, and wherein the mole equivalents of BTC:sucrose-6-ester is in the range of about 2.8:1 to about 3.5:1.