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(54) Title: NOVEL METHOD OF EXTRACTION OF 6-O-PROTECTED TRICHLOROGALACTOSE FROM THE
CHLORINATED MASS

(57) **Abrégé/Abstract:**

A process is described for extraction of 6- acyl - 4,1', 6' trichlorogalactosucrose abbreviated as TGS-6-ester from a process stream containing one or more of TGS-6-ester and impurities including DMF, requiring DMF removal, comprising neutralization of the process stream, adjustment of pH thereafter to acidic side, preferably between 5 to 7, followed by extraction with a partially miscible or immiscible organic solvent, optional concentration of the organic solvent extract, extraction of the organic solvent extracts with saturated aqueous salt solution to remove dimethylformamide (DMF) and isolation of TGS-6-acetate in a pure fraction which can be subjected to deacylation at alkaline pH to form TGS.



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(54) Title: NOVEL METHOD OF EXTRACTION OF 6-O-PROTECTED TRICHLOROGALAC TOSE FROM THE CHLORI-
NATED MASS

(57) Abstract: A process is described for extraction of 6- acyl - 4,1', 6' trichlorogalactosucrose abbreviated as TGS-6-ester from
a process stream containing one or more of TGS-6-ester and impurities including DMF, requiring DMF removal, comprising neu-
tralization of the process stream, adjustment of pH thereafter to acidic side, preferably between 5 to 7, followed by extraction with
a partially miscible or immiscible organic solvent, optional concentration of the organic solvent extract, extraction of the organic
solvent extracts with saturated aqueous salt solution to remove dimethylformamide (DMF) and isolation of TGS-6-acetate in a pure
fraction which can be subjected to deacylation at alkaline pH to form TGS.

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TITLE

NOVEL METHOD OF EXTRACTION OF 6-O-PROTECTED
TRICHLOROGALACTOSE FROM THE CHLORINATED MASS

TECHNICAL FIELD

5 The present invention relates to a novel process and a novel strategy for
purification of the sucrose-6-ester free from amide such as
dimethylformamide (DMF) by direct extraction from the reaction mixture in
process for production of chlorinated compounds including sucrose, 1'-6'-
Dichloro-1'-6'-DIDEOXY- β -Fructofuranosyl-4-chloro-4-deoxy-
10 galactopyranoside.

BACKGROUND OF THE INVENTION

Prior art literature describes the synthetic scheme to produce the 1'-6'-
Dichloro-1'-6'-DIDEOXY- β -Fructofuranosyl-4-chloro-4-deoxy-
galactopyranoside i.e. 4,1', 6' trichlorogalactosucrose (abbreviated as
15 TGS), starting from sucrose. In one of the embodiments one could protect
the 6th position of the sucrose molecule before submitting it to the
chlorination reaction. Chlorination of the sucrose-6-acetate, or any other
equivalent sucrose-6-ester, could be carried out using any of the
conventional Vilsmeier reagents prepared from phosphorus oxychloride,
20 phosphorus pentachloride, phosgene or [Bis(trichloromethyl) carbonate]
and solvents like DMF or dimethylacetamide. The difficulty in these
reactions is the isolation of the product in the protected or deprotected
form free from the solvent such as DMF used during the reaction. Various
methods are reported in the patent literature wherein the reaction mixture
25 is first quenched in an aqueous alkali solution, which could be either

subjected to steam stripping to remove only the DMF (Navia et al US patent nos. 5530106 and 5498709) or by removing all the water and the solvent in a suitable drier [Ratnam et al (2005)a (WO/2005/090374 i.e. PCT/IN2004/000142 and Ratnam et al (2005)b (WO/2005/090376) i.e. PCT/IN2004/000064). Both the methods have one drawback that during the de-protection process where the pH of the quenched mass goes up to 9 to 11, there is considerable loss in the DMF. Also if the DMF is not totally removed from the reaction mass it is carried over till the crystallization stage and hinders the crystallization process.

The present invention relates to a novel process and a novel strategy for isolation of the 6-protected trichlorogalactosucrose derivatives from the reaction mixtures obtained from the chlorination of the 6-acyl sucrose. The acyl group could be an aromatic acyl group like benzoyl, substituted aromatic acyl group such as paramethoxy benzoyl group or alkyl acyl group namely acetyl group. The 6-protected-trichlorogalactosucrose derivative could be deprotected by conventional alkaline hydrolysis to produce the desired trichlorogalactosucrose.

SUMMARY OF THE INVENTION

One embodiment of this invention relates to protecting DMF as well as TGS-6-ester from destruction by adjusting the pH of the neutralized chlorinated reaction mixture to pH 5 to 7, then extracting the same by immiscible or partially immiscible organic solvents, washing the organic solvent extract with saturated aqueous salt solution to achieve removal of DMF and recovery of the extracted organic ingredients from the organic

solvent extract by applying appropriate method of purification including but not limited to solvent extraction, column chromatography and the like.

The TGS-6-ester isolated either in crude or pure form is de-esterified at alkaline pH and TGS formed is isolated by applying one or more of a purification process.

DETAILED DESCRIPTION OF THE INVENTION

In the present embodiment a process has been developed wherein after the chlorination reaction the pH of reaction mass is adjusted to about 5 to 7 by hydroxides or carbonates of alkali, alkaline earth metals or even with alkoxides of alkali or alkaline earth metals. The neutralized mass is analyzed by TLC and it was seen that there was practically no deacetylation observed from 6-acetyl TGS (TGS-6-acetate) to TGS. The mass is then extracted with water immiscible or sparingly miscible solvents such as ethyl acetate, methyl ethyl ketone, dichloromethane, etc. All the 6-acyl trichlorogalactosucrose (TGS-6-ester) along with other chlorinated sucrose derivatives comes into the organic solvent layer.

The organic extract is concentrated to 50 % of its initial volume and is washed with saturated sodium chloride aqueous solution in order to remove DMF extracted in the organic layer. The ratio of saturated sodium chloride solution to organic extract is maintained between 1:5 to 1:7 The washing was repeated for 5 to 10 cycles It has been seen that the DMF, which is more water soluble, is retained back into the aqueous layer. Thus this methodology also gives an innovative process to remove the DMF from the reaction mixture, which is rather difficult to get rid off.

The crude TGS-6-acetate could be isolated from ethyl acetate extract. It is then purified by either extractive purification using solvents or purifying the product by column chromatography using silanized silica gel. The purified could be isolated and deacetylated either in an aqueous alkaline solution or in alcoholic alkoxide solution to give the desired trichlorogalactosucrose.

In an another strategy after the solvent extraction of the neutralized reaction mass, concentration and saturated sodium chloride washings, the impure TGS-6-ester could be deacetylated first to afford the crude trichlorogalactosucrose which is subsequently purified by either extractive purification method or by column chromatography using silanized silica gel.

Once the pure TGS is obtained from either extractive or chromatographic purification, it is crystallized by using solvent mixtures like ethyl acetate / dichloromethane, methanol / ethyl acetate, butyl acetate / dichloromethane or methanol / butyl acetate.

The examples given below are only illustrations of preferred embodiment of this invention. They shall in no way be construed to limit the scope of the invention by the actual chemicals used, by the actual reaction conditions used and the like. This invention is applicable to one or more of a process of production of TGS-6-acetate or TGS wherein DMF is a component of the process stream / Reaction Mixture and is required to be removed for making next process step possible more efficiently. Any adaptation or modification of the embodiments described here or new embodiments that are within the scope of the claims, that are obvious to

a person skilled in the art, are considered as within the scope of this specification. Similarly, any mention of singular is also meant to cover its plural also unless the context does not permit so. If the said singular word refers to a generic term / name, it also encompasses all the specific examples of that kind, unless the context does not permit so. Thus, "a solvent" covers use of all known solvents, of one or more of them, either singly, or in combination as a mixture or as used successively and "a process of purification" encompasses one or more or all the known processes applicable in the context.

Further, mention of any ester group in general, including "acyl" or in specific including "acetyl" or "acetate" shall be construed to include every chemical equivalent to that group.

Example 1

Tertiary amide removal from extracted neutralized mass by NaCl washings and subsequent purification by extractive purification

80 kg of sucrose-6-acetate was chlorinated by the Vilsmeier reagent generated by PCl_5 (252.8 kg) and DMF (480 kg). After chlorination, the reaction mass was neutralized in water and calcium hydroxide slurry was used for adjusting the pH to 6.8. The total volume after neutralization was 3500 L. After neutralization the pH was then adjusted to 5.0 using dilute HCl.

The neutralized mass was filtered through the filter press to remove extraneous solids in the solution. Then the solution was subjected to Packed column Liquid-Liquid extraction using 1:3.5 times of ethyl acetate.

The layers were separated and the respective layers were analyzed for

TGS-6-acetate content by HPLC and DMF content by GC. It was found that 93% of the 6-O-acetyl TGS was extracted into the organic layer and DMF content was found to be 1.87%.

5 The organic layer was then concentrated to 50% and was treated with 1:0.1 times of saturated NaCl solution. The layers were separated and five such washings were carried out. The DMF in the extract was reduced to less than 0.5%. The organic layer was then further concentrated for complete removal of ethyl acetate.

10 The syrup obtained was diluted to 1:2 times with water and then the pH was adjusted to 9.0 using sodium hydroxide. The Deacetylation was monitored by TLC and after stirring for 4-5 hrs, the deacetylation was completed.

The mass was filtered and neutralized with 30% Hydrochloric acid to a pH of 7.0 – 7.5.

15 The deacetylated aqueous layer was taken for extractive purification for removal of polar and non polar impurities. Partial extraction of the neutralized mass was performed with 1: 0.25 v/v of 1:1 mixture of ethyl acetate and cyclohexane so as to remove the majority of the non-polar impurities. The aqueous layer was saturated with sodium chloride and the
20 TGS was extracted back in to ethyl acetate.

The ethyl acetate extract was concentrated under vacuum to thick syrupy mass to which three times its volume of methanol was added.. Then the TGS was precipitated by addition of 1:3 times of ethyl acetate and slow removal of methanol by distillation. The crystallized product was 98.9%
25 pure and the yield obtained was 45% from the chlorination stage.

Example 2

Tertiary amide removal from extracted neutralized mass by NaCl washings and subsequent purification by column chromatography

80 kg of sucrose-6-acetate was chlorinated by the Vilsmeier reagent generated by PCl_5 . (252.8 kg) and DMF (480 kg). After chlorination, the reaction mass was neutralized using 30% sodium hydroxide solution and then the pH was again brought back to 5.0 by addition of dilute HCl. The total volume of the filtered solution was found to be 3200L. Then the solution was filtered to remove extraneous solids and was subjected to Packed column Liquid-Liquid extraction using 1:3.5 times of ethyl acetate. The organic layer was then concentrated to 50% and was treated with 1:0.1 times of saturated NaCl solution. The layers were separated and five such washings were carried out. The DMF in the extract was reduced to less than 0.5%. The organic layer was then further concentrated for complete removal of ethyl acetate.

The aqueous concentrate syrup obtained was loaded on to a SS column packed with Silanized hydrophobic silica. The quantity of silanized silica gel taken was 10 times the quantity of the aqueous concentrate taken for separation. The mobile phase used to separate the TGS from other chlorinated sucrose derivatives was aqueous buffer at pH 11.0.

The pure product fractions collected from the column chromatographic process were pooled together and concentrated by reverse osmosis membrane system up to a level of 30% concentration of TGS solution. Then the syrupy solution was extracted into ethyl acetate and was subjected to vacuum concentration and crystallization.

CLAIMS

1. A process of production of 1'-6'-Dichloro-1'-6'-DIDEOXY- β -Fructofuranosyl-4-chloro-4-deoxy-galactopyranoside abbreviated as TGS, or 6- acyl - 4,1', 6' trichlorogalactosucrose abbreviated as TGS-6-ester comprising a process stream containing one or more of TGS-6-ester, DMF, one or more of an inorganic salt, one or more of an organic salt, one or more of a caramelization product, one or more of an enzyme and the like, wherein isolation of TGS-6-ester is achieved comprising one or more of a step of:
- a. adjustment of pH of the said process stream after neutralization to acidic side, preferably between 5 to 7,
 - b. extraction of the process stream of step (a.) of this claim with a partially miscible or immiscible organic solvent comprising one or more of ethyl acetate, butyl acetate, methyl ethyl ketone, dichloromethane, toluene, cyclohexane, chloroform, and the like,
 - c. optional concentration of the organic solvent extract of step (b.) of this claim,
 - d. extraction, for one or more number of times, of the organic solvent extract of step (b) or (c.) of this claim with saturated aqueous salt solution to remove dimethylformamide (DMF) until content of residual DMF in the said organic solvent extract reduces appreciably, preferably to 0.5% or less,
 - e. subjecting the organic solvent extract at the end of step (d.) of this claim for isolation of TGS-6-acetate, or subjecting

TGS-6-acetate formed, after or before isolation and purification, to deacylation at alkaline pH to form TGS.

2. A process of step 1 wherein
 - a. the ester group of the said TGS-6-ester comprises an alkyl or an aryl group, preferably an acetate or a benzoate,
 - b. the said organic solvent used for extraction of the said process stream is ethyl acetate.
3. A process of claim 1 or 2 wherein the said process stream is a neutralized chlorination reaction mixture produced by steps comprising:
 - a. preparing a Vilsmeier Reagent of general formula $\text{HCIC}=\text{N}^{\text{sup.}+}\text{R}^{\text{sub.}2}\text{]Cl}^{\text{sup.-}}$ where R represents an alkyl group, typically a methyl or ethyl group, by one or more of a method of its preparation by reacting a tertiary amide, preferably DMF, with an acid chloride or [Bis(trichloromethyl) carbonate] ($\text{C}_3\text{O}_3\text{Cl}_6$) or carbonyl chloride (COCl_2) or thionyl chloride (SOCl_2) including a method of reacting DMF with Phosphorus Pentachloride or ethanedioyl chloride with DMF, or
 - b. preparing a Vilsmeier Reagent of formula $[\text{HPOCl}^{\text{sub.}2}\text{O.C}^{\text{sup.}+}=\text{N}^{\text{sup.}+}\text{R}^{\text{sub.}2}]\text{Cl}^{\text{sup.-}}$ where R represents an alkyl group, typically a methyl or ethyl group- by one or more of a method of its preparation by reacting a tertiary amide, preferably DMF, with phosphorus oxychloride,
 - c. reacting sucrose-6-ester solution, preferably a sucrose-6-acetate or sucrose-6-benzoate solution, made preferably in

DMF, with the said Vilsmeier reagent of the step (a.) or (b.) of this claim,

- 5
- d. heating the reaction mass to around 85°C, and maintaining the same for a period of time, preferably for about 60 minutes,
- e. then further heating to around 100°C, and maintaining the same for a period of time, preferably for about 5 hours, and
- f. then further heating to around 115°C and maintaining the same for a period of time, preferably for around 90 minutes,
- 10
- g. cooling the chlorinated mass to lower temperature, preferably around 60°C,
- h. neutralizing the said cooled chlorinated mass with an alkali, preferably by calcium hydroxide slurry in water, to around pH
- 15
- 7.0.