The present invention relates to a cost efficient process for preparation of sucralose. The present invention relates to recovery of the reagents from feed mixture obtained in various steps of sucralose. Particularly, the present invention relates to recovery of trityl chloride, β-picoline, triphenylphosphine oxide (TPPO) and methyl acetate.
Description

Title of Invention: COST EFFICIENT PROCESS FOR PREPARATION OF SUCRALOSE

Field of invention

The present invention relates to cost efficient process for preparation of sucralose. The present invention relates to recovery of the reagents from feed mixture obtained in various steps of sucralose. Particularly, the present invention relates to recovery of trityl chloride, β-picoline, triphenylphosphine oxide (TPPO) and methyl acetate.

Background of the invention

Sucralose is a potent sweetener having sweetness several hundred times that of sucrose. It is chemically known as 1,6-dichloro-1,6-dideoxy-β-D-fructofuranosyl-4-chloro-4-deoxy-α-galactopyranoside and having formula is C12H19Cl3O8 and molecular weight 397.64. Sucralose is used as sweetener in beverage, as coating tablet, chewing gum and other food products. It is marketed by McNeil under tradename Splenda®.

Process for preparation of sucralose is described in U.S. Pat. Nos. 4,783,526; 4,801,700; 4,362,869; 4,920,207; and 4,977,254; the entirety of which are incorporated herein by reference.

A process for preparing Sucralose is set forth in U.S. Pat. No.4,362,869. This process converts sucrose through a number of steps into Sucralose. This process describes the sequential steps of (1) tritylation of sucrose to block the three primary alcohol groups; (2) acetylation of the five secondary alcohol groups as acetates; (3) detritylation of the three primary alcohol groups to deblock them; (4) acetyl migration from the 4-position to the 6-position; (5) chlorinating the desired alcohol groups at positions 4, 1', 6'; and (6) deblocking the remaining five alcohol groups by deacetylation using sodium methoxide in methanol thereby yielding Sucralose.

The schematic representation is as given below (Scheme I)
The reagents used in the process for preparation of sucralose are costly and for commercial manufacture, it is required to be recovered to reduce the overall cost of Sucralose. Some of such valuable costly reagents are trityl chloride, β-picoline, triphenyl phosphine oxide, and solvent methyl acetate. Thus, methods of recovering and reusing of the reagents from a sucralose manufacturing process would be of significant value.

The trityl groups are typically introduced via reaction with a trityl halide, such as trityl chloride. The reaction is usually promoted by the inclusion of an amine such as pyridine or pyridine derivative such as picoline to neutralize the HCl liberated by the tritylation reaction. As seen above, the role of the trityl moiety is played in the first three steps of the process: (1) tritylation of sucrose to form 6,1',6’ tri-O-trityl sucrose (TRIS), (2) acetylation of the TRIS to form 6,1’,6’ tri-O-trityl sucrose pentaacetate (TRISPA), and (3) detritylation of the TRISPA to form 2,3,4,3’,4’ penta-O-acetyl sucrose (4-PAS).

Importantly, the overall stoichiometry of this 3-step sequence results in no net consumption of trityl groups, which are essentially 'borrowed' by the sucrose for use during step 2 and released again in step 3. In practice, however, there is potential for extensive loss of trityl groups in the overall process due to the formation of tritylated
sucrose byproducts and tritylated sucrose ester byproducts.

[19] The tritylation reaction and subsequent workup typically produces not only the desired tritylated product (TRIS), but also some unwanted tritylated sucrose byproducts. Such byproducts may for example have trityl groups in the wrong numbers and/or at the wrong positions on the sucrose molecule. Trityl alcohol is also formed from any excess trityl chloride.

[20] Trityl chloride recovery is disclosed in WO2008070043. The process involves recovery of triarylmethyl halide from a reaction mixture obtained after triarylmethylation and acetylation reaction which comprise separating triarylmethyled sucrose ester byproduct from the TRISPA and reacting the byproduct with hydrogen halide to cleave triaryl methyl group. Triaryl methyl component is treated with hydrogen halide and triarylmethyl halide is recovered.

[21] β-picoline is used as base in the tritylation and acetylation reaction which is also an expensive reagent and needs to be recovered and reused.

[22] Triphenyl phosphine oxide (TPPO) is used in chlorination step to form complex with acid chloride such as thionyl chloride or phosgene, triphenyl phosphine oxide is costly reagent and required to be recovered and reused.

[23] US4783526 discloses a process for preparation of sucralose in which TPPO is recovered in chlorination step. In this process after completion of the chlorination reaction, aqueous solution of sodium bicarbonate is added to the chlorinated reaction mixture and organic layer is separated. Methyl isobutyl ketone or ether is added to the organic layer, cooled to 0°C whereby TPPO precipitate out which is recovered by filtration. However, in this process recovery is less.

[24] It is therefore, a need to develop an improved process for preparation of Sucralose in which expensive reagents are recovered in efficient manner and reused. Simultaneously, the recovery process should be easy, simple and industrially applicable and cost efficient.

[25] The present inventors have directed their research work towards developing an improved process for preparation of Sucralose in which the valuable expensive reagents used in various reaction steps is recovered and reused. They directed their research work towards the recovery of trityl chloride, β-picoline, triphenylphosphine
oxide and solvent methyl acetate which is used for crystallization of sucralose.

[33] The inventors have found that trityl groups may typically be expected to distribute between product (TRISPA) and tritylated sucrose byproducts in an approximately 70:30 ratio. If the byproducts are removed after tritylation and again after acetylation, it results in wastage of trityl group. The present inventors found that if trityl chloride is recovered from the feed obtained after the detritylation reaction, it will turn into getting more percent yield recovery of trityl chloride. They developed a novel process for the recovery of trityl chloride from the feed obtained after detritylation step. The present inventors also developed a process for recovery of β-picoline from the aqueous solution obtained after the work up of the tritylation and acetylation reaction. They observed that β-picoline can be distilled out with water azeotropically. They utilized this physical parameter for the recovery of β-picoline. The present inventors also developed a process for recovery of triphenylphosphine oxide (TPPO) from the toluene layer obtained from the chlorination reaction step. They also recovered the methyl acetate obtained from sucralose crystallization step.

[35] [36] Object of the invention

[37] A primary object of the present invention is to provide a process for recovery of Trityl chloride from a reaction mixture obtained after detritylation reaction.

[38] Another object of the present invention is to provide a process for recovery of β-picoline from a reaction mixture obtained after tritylation and acetylation reaction.

[39] Another object of the present invention is to provide a process for recovery of triphenyl phosphine oxide from a reaction mixture obtained after chlorination reaction.

[40] Another object of the present invention is to provide a process for recovery of methyl acetate from sucralose crystallization step.

[41] Yet another object of the present invention is to provide cost efficient process for preparation of sucralose.

[42] Summary of the invention

[43]
Accordingly, in one aspect, the present invention provides a process for recovery of Trityl chloride comprising steps of:

(i) refluxing the toluene layer containing trityl chloride and other trityl byproducts with sodium hydroxide;

(ii) adding water to the above solution obtained in step (i) and heating at elevated temperature

(iii) separating organic layer from step (ii) and dehydrating it

(iv) refluxing the dehydrated organic layer with acetyl chloride

(v) removing solvent from the mixture obtained in step (iv) to get residue

(vi) dissolving residue in pet ether and charcoalizing it and filtering it

(vii) removing solvent from filtrate to give trityl chloride

In another aspect, the present invention provides a process for recovery of β-picoline comprising steps of:

(i) heating the aqueous layer containing β-picoline with calcium hydroxide;

(ii) distilling the solution obtained in step (i) to recover β-picoline with water as distillate;

(iii) adding toluene to the distillate obtained in step (ii) containing β-picoline and water and removing water azeotropically;

(iv) evaporating toluene from the toluene layer obtained after step (iii).

In another aspect, the present invention provides a process for recovery of triphenylphosphine oxide (TPPO) comprising steps of:

(i) heating the toluene layer containing TPPO and trace amount of 4,r,6'-trichloro-4,r,6'-trideoxygalactosucrose pentaacetate (TOSPA) with sodium hydroxide and methanol;

(ii) adding water to the reaction mixture obtained in step (i) and separating toluene layer;

(iii) washing the toluene layer with water;

(iv) distilling out approximately 80% volume of toluene from toluene layer to give TPPO rich concentrate;

(v) cooling TPPO rich concentrate to give precipitates of TPPO;

(vi) filtering the precipitates to give solid TPPO.

In another aspect, the present invention provides a process for recovery of methyl acetate comprising steps of:

(i) refluxing mixture of methyl acetate and methanol with acetic anhydride;

(ii) monitoring the reaction on GC for methanol content;

distilling methyl acetate atmospherically
**Brief description of the drawings**

- Fig. 1 is a schematic process flow diagram of a method for recovering tritryl chloride according to the invention.
- Fig. 2 is a schematic process flow diagram of a method for recovering β-picoline according to the invention.
- Fig. 3 is a schematic process flow diagram of a method for recovering TPPO according to the invention.
- Fig. 4 is a schematic process flow diagram of a method for recovering methyl acetate according to the invention.

**Detailed description of the invention**

The synthetic scheme for preparation of sucralose is as shown below (Scheme II).

**Scheme II**

A process for preparation of sucralose comprising steps of:

- (a) tritylaing the sucrose using trityl chloride in the presence of β-picoline to form 6,1',6'-tri-O-tritylsucrose (TRIS) and tritylated sucrose byproducts;
- (b) acylating the 6,1',6'-tri-O-tritylsucrose (TRIS) using acetic anhydride in the presence of β-picoline to form a 6,1',6'-tri-O-tritylsucrose pentaester (TRISPA) and tritylated sucrose ester byproducts;
- (c) recovering β-picoline from step (b);
- (d) passing dry HCl to TRISPA and tritylated sucrose ester byproducts to produce
2,3,4,3',4'-penta-O-acetyl sucrose (4-PAS) and other unreacted tritylated sucrose ester byproducts, acetyl sucrose byproducts, trityl chloride and tritanol;

(e) recovering trityl chloride from step (d);

(f) reacting 4-PAS with t-butyamine to give 2,3,6,3',4'-penta-O-acetyl sucrose (6-PAS);

(g) chlorinating 6-PAS with thionyl chloride in the presence of TPPO to give 4,1',6'-tichloro-4,r,6'-trideoxy galactosucrose pentaacetate (TOSPA);

(h) recovering TPPO from step (g);

(i) deacetylating TOSPA with sodium methoxide in methanol to give sucralse;

(j) crystallizing sucralse from methyl acetate;

(k) recovering methyl acetate from step (j).

In the above process for preparation of sucralse, trityl chloride is recovered from toluene layer containing trityl chloride and other trityl byproducts obtained from detritylation step. A solution of 6,1',6'-tri-O-tritylsucrose pentaester (TRISPA) in toluene is detritylated by passing dry HCl (g). Aqueous sodium bicarbonate solution is added to the reaction mixture, stirred well and both the layers are separated. Aqueous layer is taken for the recovery of 2,3,4,3',4'-penta-O-acetyl sucrose (4-PAS) whereas toluene layer is taken for the recovery of trityl chloride.

A process for recovery of Trityl chloride comprising steps of:

(i) refluxing the toluene layer containing trityl chloride and other trityl byproducts with sodium hydroxide;

(ii) adding water to the above solution obtained in step (i) and heating at elevated temperature;

(iii) separating organic layer from step (ii) and dehydrating it;

(iv) refluxing the dehydrated organic layer with acetyl chloride;

(v) removing solvent from the mixture obtained in step (iv) to get residue;

(vi) dissolving residue in pet ether and charcoalising it and filtering it;

(vii) removing solvent from filtrate to give trityl chloride.

Toluene layer obtained from detritylation step is heated with D.M. water at about 85°C to about 90°C for about 30 min. The aqueous and toluene layers are separated. The detritylated sucrose derivatives or such sugar impurities are removed in aqueous layer. This process is repeated to obtain relatively pure toluene layer which is rich with trityl derivative. This toluene layer is refluxed with sodium hydroxide flakes for about 2 to 2.5 hours. This reaction converts all trityl derivative into trityl alcohol. D.M. water was added to the reaction mixture and it is further heated at about 85°C to about 90°C for about 30 min. The aqueous and toluene layers are separated. The toluene layer
contains major portion of trityl alcohol whereas all other salts generated and sucrose
derivatives are removed in aqueous layer. This process is repeated further two times
and the toluene layer as obtained is dehydrated azeotropically to remove moisture from
toluene layer. Acetyl chloride is added to the dehydrated toluene layer and refluxed for
about 2 to 2.5 hours. This reaction converts trityl alcohol into trityl chloride. Toluene
was distilled out completely from the reaction mixture and Pet ether of boiling range
80-100 is added. To the reaction mass, activated charcoal was added and heated at
about 75° to about 78°C for 30 minutes. The reaction mixture was filtered through
cartridge filter. The filtrate was evaporated to dryness to give molten trityl chloride
which is transferred to flaker to get the flakes of trityl chloride. This recovered trityl
chloride can be reused in tritylation reaction of sucrose.

β-picoline is recovered form the aqueous solution obtained after the work up of the
tritylation and acetylation reaction. Sucrose is tritylated using trityl chloride in the
presence of β-picoline and catalytic amount of DMAP. After completion of tritylation
on TLC, acetic anhydride is added to the reaction mixture to acetylate the remaining
free hydroxyl groups of sucrose. After completion of the acetylation reaction, toluene
and D.M. water was added to the reaction mixture and cooled to 10°C. Cone. HCl was
added to the reaction mixture and stirred well. The aqueous layer and toluene layers
are separated. Toluene layer is taken for the recovery of 6,1',6'-tri-O-tritylsucrose
pentaester (TRISPA) whereas aqueous layer is taken for the recovery of β-picoline.

A process for recovery of β-picoline comprising steps of:

(i) heating the aqueous layer containing β-picoline with calcium hydroxide;
(ii) distilling the solution obtained in step (i) to recover β-picoline with water as
distillate;
(iii) adding toluene to the distillate obtained in step (ii) containing β-picoline and
water and removing water azeotropically;
(iv) evaporating toluene from the toluene layer obtained after step (iii).

The aqueous layer obtained from acetylation step contains β-picoline as its hy-
drochloride salt. On heating the aqueous layer with calcium hydroxide, β-picoline gets
free as base from its hydrochloride salt. Fresh D.M. water is added to the reaction
mixture and distilled, β-picoline distill out with water at vapor temperature 97-99°C
and is collected as distillate. To this distillate, toluene is added and water is removed
azeotropically using dean stark apparatus. Finally, the toluene containing β-picoline is
also distilled to get β-picoline as residual liquid. This recovered β-picoline can be
reused in tritylation and acetylation steps of sucralose.
Triphenylphosphine oxide (TPPO) is recovered from the toluene layer obtained from the chlorination reaction step.

Thionyl chloride is added to slurry of 6-PAS and TPPO in toluene heated at 110°C. After completion of chlorination reaction, the mixture was cooled and basified with Aq. Sodium acetate solution. Sodium bicarbonate was added to it and stirred well. The product 4,1',6'-trichloro-4,1',6'-trideoxy galactosucose pentaacetate (TOSPA) was filtered and washed with cold water. The filtrate was containing toluene layer as well as aq. layer. Aq. layer was discarded and toluene layer was taken for recovery of TPPO.

A process for recovery of triphenylphosphine oxide (TPPO) comprising steps of:

(i) heating the toluene layer containing TPPO and trace amount of 4,1',6'-trichloro-4,1',6'-trideoxy galactosucose pentaacetate (TOSPA) with sodium hydroxide and methanol;

(ii) adding water to the reaction mixture obtained in step (i) and separating toluene layer;

(iii) washing the toluene layer with water;

(iv) distilling out approximately 80% volume of toluene from toluene layer to give TPPO rich concentrate;

(v) cooling TPPO rich concentrate to give precipitates of TPPO;

(vi) filtering the precipitates to give solid TPPO.

The toluene layer contains TPPO as well as trace amount of TOSPA. Toluene layer is heated with sodium hydroxide and methanol at about 50° to about 55°C for about 2 hours. This reaction converts trace amount of TOSPA to sucralose. D.M. water is added to the reaction mixture and stirred for 30 min. The aqueous and toluene layers are separated. To the toluene layer D.M. water is added and stirred for 30 min. Toluene layer is separated and distilled approximately 80% of its original volume. The concentrated toluene solution is gradually cooled to 0°C and maintained at the same temperature for about one to one and a half hour whereby TPPO precipitates out. The solid is filtered, washed with chilled toluene and suck dried. This recovered TPPO can be reused in chlorination step of sucralose.

Methyl acetate is recovered from sucralose crystallization step. After deacylation of TOSPA with sodium methoxide, the reaction mixture is neutralized with H+ resin, charcoalized and then methanol was evaporated to dryness. To the oily product, methyl acetate is added and methyl acetate is azeotropically distilled with methanol. From the residue, sucralose is crystallized whereas the distillate containing methyl acetate and methanol is taken for the recovery of methyl acetate.
A process for recovery of methyl acetate comprising steps of:

(i) refluxing mixture of methyl acetate and methanol with acetic anhydride;
(ii) monitoring the reaction on GC for methanol content;
(iii) distilling methyl acetate atmospherically.

The mixture of methyl acetate and methanol is refluxed with acetic anhydride. The amount of acetic anhydride is calculated from the following formula.

\[
\text{Amount of Acetic anhydride per ml of Mixture (X) = (Area \% of Methanol by GC x 0.03026 x 100)} \text{ g}
\]

The reaction is monitored on GC for methanol content which should not be more than 0.2%. If methanol content is more, then added 10% more acetic anhydride of the quantity and refluxed. Methyl acetate is distilled out atmospherically. This recovered methyl acetate can be reused for crystallization of sucralose.

The process of the present invention is described by the following examples, which are illustrative only and should not be construed so as to limit the scope of the invention in any manner.

**Example-1**

**Preparation of Sucralose**

(a) **Preparation of 6, 1', 6'-Tri-O-tritylsucrose pentaacetate (TRISPA)**

A mixture of Sucrose (12kg) and β-picoline (36kg) was heated at 50°C to 55°C and catalytic amount of dimethylamino pyridine (DMAP) was added. Trityl chloride (31.2kg) was added in 3 portions at the interval of 1.5hr. The reaction mass was stirred for 8 to 10 hrs at 50°C to 55°C. After completion of the reaction, it was cooled to 30°C and acetic anhydride sufficient for acetylation was added to and heated to 50°C to 55°C for 5hr. The progress of the reaction was monitored on TLC. The reaction mixture was cooled to room temperature. Toluene (100L) and water (24L) was added to the reaction mixture and cooled to 10°C. Cone. HCl (33.5kg) was added at 10°C. β-picoline content was checked in organic layer. Aqueous layer was separated which is extracted with toluene. Combined toluene layer was washed twice with 20% w/w sodium chloride solution. The aqueous layer was transferred for recovery of β-picoline. The organic layer was dehydrated and taken as such for detritylation step.

(b) **Preparation of 2, 3, 4, 3', 4'-Penta-O-acetylsucrose (4-PAS)**

A solution of TRISPA in Toluene obtained in example-1 was cooled to 0°C under N₂ atmosphere. Dry HCl(g) was bubbled slowly through reaction at the same temperature for 3 to 4 hr. The progress of the reaction was monitored on TLC. Sodium
carbonate (32kg) in Water (67L) was added to the reaction mixture at 10°C to 25°C during 30min and stirred for 20 min. Both layers were separated. Aq. layer was washed with toluene (10L). The pH of aq. layer was adjusted to 7 to 7.5 with sodium bi-carbonate (6.5kg) at 15°C and stirred for 20min. Dichloromethane (20L) was added and extracted. Organic layer was separated. Sodium chloride (18kg) was added to the aqueous layer, stirred for 10 min and then extracted with Dichloromethane (8L). Organic layer was separated. Both organic layers were combined and filtered through cartridge. The clear organic layer was evaporated to dryness. A mixture of ethyl-lactate: hexane (7:3) (2L) was added to the residue and again distilled out to give 4-PAS and it was taken further for migration step.

(c) Preparation of 2, 3, 6, 3', 4'-Penta-O-acetylsucrose (6-PAS)

A mixture of ethyl acetate: hexane (7:3) (30L) was added to 4-PAS obtained in the example-2. The reaction mixture was heated to 660°C to 670°C and dehydrated. The reaction mixture was cooled to 50°C and t-Butyl amine (0.5L) was added. The reaction mixture was stirred for 5hr at 50°C to 55°C. After completion of conversion to 6-PAS, the reaction mixture was cooled to 30°C and stirred at the same temperature for 2hr. The solid was filtered, washed with mixture of ethylacetate: Hexane. The product was dried at 55°C to 65°C till constant weight obtained (8.0 kg).

(d) Preparation of 4,1,6'-trichloro-4,1,6'-trideoxygalactosucrose pentaacetate (TOSPA)

To slurry of 6-PAS (7.0kg) and triphenyl phosphine oxide (TPPO) in toluene (21.0L) was added thionyl chloride (32.8 ml) and the mixture was heated at 110°C within 2.5 hr and maintained for 2.5 hr. The reaction was monitored on TLC. After completion of reaction, the mixture was cooled to 70°C. Aq. Sodium acetate solution was added to the reaction mixture at 10-15°C within 20-30min and stirred for 20-30min. Sodium bi-carbonate (3.5kg) was added to it within 20min and stirred for 30min. The product was filtered and washed with cold water (2.0L). The filtrate is settled and both aqueous and organic layers were separated. The organic layer (i.e. toluene layer) is taken for TPPO recovery. The wet cake is charged to toluene (21.0L) and water (21.0L) and heated to 70-75°C and stirred for 10-15min. The toluene layer is separated and washed with hot water. The toluene layer is dehydrated to remove traces of water and filtered through line filter at 70-75°C. It is cooled to 10°C. The compound is filtered and washed with chilled toluene, suck dried and dried in oven (5.5 kg).

(e) Preparation of Sucralose

TOSPA (100 g) is stirred at 20°C with sodium methoxide (30%) (3ml) in methanol
(250 ml) for 2 hours at 20°C±2°C. TOSPA dissolves within 10 mins. The completion of reaction is monitored on TLC. The solution is neutralized by stirring with (H+) resin (10g). The resin is removed by filtration and washed with methanol (25 ml), the filtrate and wash then being stirred with decolorizing charcoal (4 g) for 30 mins at 20°C. The solution is filtered through hyflow bed followed by membrane filter to remove any carbon particles. Total filtrate was distilled to remove methanol. Trace amount of methanol was removed by vacuum distillation. To the oily product, methyl acetate was added and distilled out methylacetate and methanol azeotropically. The reaction mixture was cooled to 10°C over one hour. The precipitate was filtered, washed with methyl acetate and suck dried. The solid was dried in vacuo at 40°C for 12 hours to give solid (50 g).

Example-2

Recovery of trityl chloride

D.M. water (12 L) was added to the toluene layer (155L) containing trityl chloride and other trityl byproducts obtained from detritylation step and heated to 85-90°C for 30 minutes. The organic layer was separated and again D.M. water (12 L) was added and repeated the process. The organic layer was separated. NaOH flakes (1.7 Kg) was added to it and heated to reflux for 2 hours. The absence of sucrose derivative is checked by TLC. D.M. water (12 L) was added slowly to the reaction mixture and heated at 85-90°C for 30 minutes. The organic layer was separated and again D.M. water (12 L) was added and repeated the process for further 2 times. The organic layer was separated, dehydrated azeotropically to remove residual moisture and cooled to 38-40°C. Acetyl chloride, (11.04 Kg) was added over 30 minutes between the temperature 40-45°C. The reaction mixture was heated to reflux for 2 hours. Toluene was distilled out completely applying high vacuum. The reaction mass was cooled to 100-105°C and Pet ether 80-100 (87 L) was added to it and stirred for 10 min. The mixture was heated at 75-78°C. Activated charcoal (500 g) was added and stirred at 75-78°C for 30 minutes. The reaction mass was filtered through cartridge filter at the same temperature and the cartridge was washed with Pet ether 80-100 (5 L). Pet ether was distilled out completely applying high vacuum. Molten Trityl chloride is collected and charged to flaker to get flakes of Trityl Chloride (12.71 Kg)

Yield: 84.7%

Example-3

Recovery of β-picoline

A mixture of D.M. water (1200 ml) and calcium hydroxide powder (600 g) was heated to 95°-100°C. The aqueous solution (500 g) obtained after the work up of the
tritylation and acetylation reaction containing β-picoline was added drop wise at reflux (100°C) to the above prepared calcium hydroxide solution. Fresh D.M. water (500 ml) was added to it. The remaining aqueous layer (2.5 Kg) was added dropwise over period of two and a half hours. The reaction mixture was distilled, β-picoline was distilled out with water at vapor temperature 97-99°C. The distillate (1800 g) was collected and checked for moisture content and β-picoline content. The distillate was dehydrated using three and a half feet pack column assembly with dean stark apparatus by adding toluene (125 ml) to the distillate and azeotropically distilling it at reflux (vapor temperature 100°C) and separating out the water (approximately 1 to 1.1 L). The remaining toluene was distilled out at vapor temperature 110-140°C to get toluene distillate (140-150OmIl). The remaining residual liquid was analysed which is β-picoline (730 g).

Example-4

Recovery of Triphenylphosphine oxide (TPPO)

After completion of chlorination reaction, the mixture was cooled and basified with Aq. Sodium acetate solution. Sodium bicarbonate was added to it and stirred well. The product 4,1′,6′-trichloro 4,1′,6′-trideoxy galactosucrose pentaacetate was filtered and washed with cold water. The filtrate was containing toluene layer as well as aq. Layer. Aq. Layer was discarded and toluene layer was taken for TPPO recovery.

NaOH Flakes (10.0 g) and methanol (50.0 ml) was added to the toluene layer (1.0 L) containing TPPO obtained from chlorination step and heated to 50-55°C for 2 hours. D.M. water (300.0 ml) was added to the reaction mixture and stirred for 30 minutes. The organic layer was separated and D.M. water (100.0 ml) was added and stirred well. The organic layer was separated and distilled out. Approximately 800 ml of toluene was distilled out. The remaining solution was cooled gradually to 0°C and maintained for 1 hour. The solid compound was filtered, washed with chilled toluene (20.0 ml) and suck dried. The solid was dried to give TPPO (25.0 g). The mother liquor toluene was transferred for toluene recovery.

Example-5

Recovery of Methyl acetate

Acetic anhydride (X gm) was added to a mixture of Methyl acetate and Methanol mixture (100 ml) obtained from deacetylation step and heated to reflux at 65-75 °C for 6-7 hours. The reaction mixture was monitored by GC for methanol content which should not be more than 0.2%. If the content is more then added 10 % more acetic anhydride of the quantity and refluxed. Methyl acetate was atmospherically distilled at
56-59° C and methanol content was periodically checked. Pure Methyl acetate (100 ml) is obtained.

Amount of Acetic anhydride per ml of Mixture (X) = (Area % of Methanol by GC x 0.03026 x 100) g.
Claims

[Claim 1] 1. A process for recovery of Trityl chloride comprising steps of:
(i) refluxing the toluene layer containing trityl chloride and other trityl byproducts with sodium hydroxide;
(ii) adding water to the above solution obtained in step (i) and heating at elevated temperature;
(iii) separating organic layer from step (ii) and dehydrating it;
(iv) refluxing the dehydrated organic layer with acetyl chloride;
(v) removing solvent from the mixture obtained in step (iv) to get residue;
(vi) dissolving residue in pet ether and charcoalising it and filtering it;
(vii) removing solvent from filtrate to give trityl chloride.

[Claim 2] 2. A process for recovery of β-picoline comprising steps of:
(i) heating the aqueous layer containing β-picoline with calcium hydroxide;
(ii) distilling the solution obtained in step (i) to recover β-picoline with water as distillate;
(iii) adding toluene to the distillate obtained in step (ii) containing β-picoline and water and removing water azeotropically;
(iv) evaporating toluene from the toluene layer obtained after step (iii).

[Claim 3] 3. A process for recovery of triphenylphosphine oxide (TPPO) comprising steps of:
(i) heating the toluene layer containing TPPO and trace amount of 4,1',6'-trichloro-4,1',6'-trideoxygalactosucrose pentaacetate (TOSPA) with sodium hydroxide and methanol;
(ii) adding water to the reaction mixture obtained in step (i) and separating toluene layer;
(iii) washing the toluene layer with water;
(iv) distilling out approximately 80% volume of toluene from toluene layer to give TPPO rich concentrate;
(v) cooling TPPO rich concentrate to give precipitates of TPPO;
(vi) filtering the precipitates to give solid TPPO.

[Claim 4] 4. A process for recovery of methyl acetate comprising steps of:
(i) refluxing mixture of methyl acetate and methanol with acetic anhydride;
(ii) monitoring the reaction on GC for methanol content;
(iii) distilling methyl acetate atmospherically.
[Claim 5] 5. A process for preparation of sucralose comprising steps of:
(a) tritylaing the sucrose using trityl chloride in the presence of \(\beta\)-picoline to form 6,1',6'-tri-O-tritylsucrose and tritylated sucrose byproducts;
(b) acylating the 6,1',6'-tri-O-tritylsucrose using acetic anhydride in the presence of \(\beta\)-picoline to form a 6,1',6'-tri-O-tritylsucrose pentaester and tritylated sucrose ester byproducts;
(c) recovering \(\beta\)-picoline from step (b);
(d) passing dry HCl to 6,1',6'-tri-O-tritylsucrose pentaester and tritylated sucrose ester byproducts to produce 2,3,4,3',4'-penta-O-acetyl sucrose and other unreacted tritylated sucrose ester byproducts, acetyl sucrose byproducts, trityl chloride and tritanol;
(e) recovering trityl chloride from step (d);
(f) reacting 2,3,4,3',4'-penta-O-acetyl sucrose with t-butylamine to give 2,3,6,3',4'-penta-O-acetyl sucrose;
(g) chlorinating 2,3,6,3',4'-penta-O-acetyl sucrose with thionyl chloride in the presence of TPPO to give 4,r,6'-tirchloro-4,l',6'-trideoxy galactosucrose pentaacetate;
(h) recovering TPPO from step (g);
(i) deacetylating 4,r,6'-tirchloro-4,l',6'-trideoxy galactosucrose pentaaacetate with sodium methoxide in methanol to give sucralose;
(j) crystallizing sucralose from methyl acetate;
(k) recovering methyl acetate from step (j).

[Claim 6] 6. A process for preparation of sucralose comprising a step of recovering \(\beta\)-picoline, the process comprising steps of:
(i) heating the aqueous layer containing \(\beta\)-picoline with calcium hydroxide;
(ii) distilling the solution obtained in step (i) to recover \(\beta\)-picoline with water as distillate;
(iii) adding toluene to the distillate obtained in step (ii) containing \(\beta\)-picoline and water and removing water azeotropically;
(iv) evaporating toluene from the toluene layer obtained after step (iii).

[Claim 7] 7. A process for preparation of sucralose comprising a step of recovering trityl chloride, the process comprising steps of:
(i) refluxing the toluene layer containing trityl chloride and other trityl byproducts with sodium hydroxide;
(ii) adding water to the above solution obtained in step (i) and heating at elevated temperature;
(iii) separating organic layer from step (ii) and dehydrating it;
(iv) refluxing the dehydrated organic layer with acetyl chloride;
(v) removing solvent from the mixture obtained in step (iv) to get residue;
(vi) dissolving residue in pet ether and charcoalising it and filtering it;
(vii) removing solvent from filtrate to give trityl chloride.

[Claim 8]
8. A process for preparation of sucralose comprising a step of recovering TPPO, the process comprising steps of:
(i) heating the toluene layer containing TPPO and trace amount of 4,1',6'-trichloro-4,1',6'-trideoxygalactosucrose pentaacetate (TOSPA) with sodium hydroxide and methanol;
(ii) adding water to the reaction mixture obtained in step (i) and separating toluene layer;
(iii) washing the toluene layer with water;
(iv) distilling out approximately 80% volume of toluene from toluene layer to give TPPO rich concentrate;
(v) cooling TPPO rich concentrate to give precipitates of TPPO;
(vi) filtering the precipitates to give solid TPPO.

[Claim 9]
9. A process for preparation of sucralose comprising a step of recovering methyl acetate, the process comprising steps of:
(i) refluxing mixture of methyl acetate and methanol with acetic anhydride;
(ii) monitoring the reaction on GC for methanol content;
(iii) distilling methyl acetate atmospherically.

[Claim 10]
10. A process for recovery of Trityl chloride as shown in schematic process flow diagram depicted in Fig. 1.

[Claim 11]
11. A process for recovery of β-picoline as shown in schematic process flow diagram depicted in Fig. 2.

[Claim 12]
12. A process for recovery of TPPO as shown in schematic process flow diagram depicted in Fig. 3.

[Claim 13]
13. A process for recovery of Methyl acetate as shown in schematic process flow diagram depicted in Fig. 4.
Fig. 1
NaOH flakes & methanol → Toluene layer containing TPPO & trace amount TOSPA

Heat at 50-55°C → Toluene layer containing TPPO, sugar byproduct, methanol & NaOH

D.M. water → Separate layers → Aqueous layer

D.M. water → Toluene layer → Separate layers → Aqueous layer

Toluene layer → Distillation → Toluene (85% of original volume)

Concentrated Toluene layer → Cooled to 0°C & Filter

Filtrate → TPPO

Fig. 3
Acetic anhydride → Methyl acetate + Methanol

Reflux at 65-75°C

GC analysis for methanol content (should be NMT 0.2%)

Distillation (atmospherically)

Methyl acetate

Fig. 4