acid. No yield and also no analytical data is given of any amounts of sorbitol or of isosorbide in the product.

A reworking of this example as disclosed herein under "Comparative Example 1" showed inter alia, that the product is a sticky liquid, the yield is very low with 9.6% and there are still considerable amounts of D-sorbitol (ca. 28%) and of isosorbide (2.5%) in the product.

US 2016/0130277 A1 (US'277) discloses in Example 1 the dehydration of Sorbitol to provide 1,4-sorbitan. The reported yield of 35% is significantly lower than the yield of 52.6 % of inventive Example 1.

Reworking of this Example 1 of US'277, as reported herein under Comparative Example 2, was not possible. In particular the crystallization of the reported residue after the reaction from cold methanol was not possible even though the procedure as reported in Example 1 US'277 up to this point was follow literally. The analysis of the this residue shows a significantly higher relative content of sorbitol and a significantly lower relative content of 1,4 sorbitan compared to the analysis of the equivalent intermediate in the clear solution in ethanol in the inventive example 1. This difference in the relative amounts of 1,4 sorbitan and sorbitol correlates well with the reported significantly lower yield of Example 1 of US'277. The reaction in Example 1 of US'277 is done under a pressure of 50 bar.

Any use of a compound for or in pharmaceutical applications requires a defined purity and usually also a high purity.

There was a need for a method for preparation 1,4-sorbitan with high yield, high purity, low content of isosorbide or D-sorbitol; the method should be as economic as possible, such as with a low number of steps such as filtration or with a low number of different chemicals used, also the method should be suited to be done "in one pot", meaning that only one reactor can be used.

In an aspect, there is provided a method for preparation of 1,4-sorbitan with four consecutive steps STEP1, STEP2, STEP3 and STEP4, wherein

in STEP1 D-sorbitol is dehydrated in a dehydration reaction DEHYDREAC in the presence of p-toluenesulfonic acid and tetrabutylammonium bromide,

the reaction time TIME1-1 of DEHYDREAC is from 3 to 12 h;

DEHYDREAC is done at a temperature TEMP1, TEMP1 is from 95 to 130 °C,

DEHYDREAC is done at a pressure PRESS1 of 500 mbar or below,
STEP1 provides a mixture MIX1;
in STEP2 ethanol is mixed with MIX1, STEP2 provides a mixture MIX2;
in STEP3 isopropanol is mixed with MIX2, STEP3 provides a mixture MIX3;
in STEP4 1,4-sorbitan is isolated from MIX3.

Unexpectedly, a method was found which gives high yield, high purity, low content of isosorbide, low content D-sorbitol; the method is economic, has a low number of steps such as filtration and uses a low number of different chemicals. The method can be done in one reactor. The method provides 1,4-sorbitan with considerable higher yields and purity compared to the example [0028] S1 of CN 106167476 A.

Claims

1. A method for preparation of 1,4-sorbitan with four consecutive steps STEP1, STEP2, STEP3 and STEP4, wherein
in STEP1 D-sorbitol is dehydrated in a dehydration reaction DEHYDREAC in the presence of p-toluenesulfonic acid and tetrabutylammonium bromide,
the reaction time TIME1-1 of DEHYDREAC is from 3 to 12 h;
DEHYDREAC is done at a temperature TEMP1, TEMP1 is from 95 to 130 °C,
DEHYDREAC is done at a pressure PRESS1 of 500 mbar or below,
STEP1 provides a mixture MIX1;
in STEP2 ethanol is mixed with MIX1, STEP2 provides a mixture MIX2;
in STEP3 isopropanol is mixed with MIX2, STEP3 provides a mixture MIX3;
in STEP4 1,4-sorbitan is isolated from MIX3.

2. The method according to claim 1, wherein
the p-toluene sulfonic acid is used in form of p-toluenesulfonic acid monohydrate.

3. The method according to claim 1 or 2, wherein
DEHYDREAC is done neat, that is only the three components D-sorbitol, p-toluenesulfonic acid and tetrabutylammonium bromide are used for and are charged for DEHYDREAC.

4. The method according to one or more of claims 1 to 3, wherein
DEHYDREAC is done at a temperature TEMP1, TEMP1 is from 95 to 120°C.

5. The method according to one or more of claims 1 to 4, wherein
the reaction time TIME1-1 of DEHYDREAC is from 4 to 12 h.

6. The method according to one or more of claims 1 to 5, wherein
DEHYDREAC is done at a pressure PRESS1 of 250 mbar or below.

7. The method according to one or more of claims 1 to 6, wherein
water is removed during DEHYDREAC.

8. The method according to one or more of claims 1 to 7, wherein

STEP2 is done at a temperature TEMP2 of from 60 to 90°C.

9. The method according to one or more of claims 1 to 8, wherein
STEP3 is done at a temperature TEMP3-1 of from 10 to 30°C.

10. The method according to one or more of claims 1 to 9, wherein
after the mixing of isopropanol, STEP3 comprises a cooling COOL3 of MIX3 to a temperature TEMP3-2 of from -5 to 5°C.

11. The method according to one or more of claims 1 to 10, wherein
STEP3 comprises a stirring STIRR3 of MIX3, STIRR3 is done for a time TIME3-2, TIME3-2 is from 1 to 12 h.

12. The method according to claim 11, wherein
STIRR3 is done after COOL3, with COOL3 as defined in claim 10.

13. The method according to claim 11 or 12, wherein
STIRR3 is done at TEMP3-2, with TEMP3-2 as defined in claim 10.

14. The method according to one or more of claims 1 to 13, wherein
1,4-sorbitan is isolated in STEP4 from MIX3 by filtration.

15. The method according to one or more of claims 1 to 14, wherein
STEP1, STEP2 and STEP3 are done consecutively in one and the same reactor.