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# ENVIRONMENTALLY FRIENDLY PURIFICATION OF DIACETONE-α-D-GLUCOSE

# VIDEI DRAUDZĪGA DIACETON- α -D-GLIKOZES ATTĪRĪŠANAS METODE

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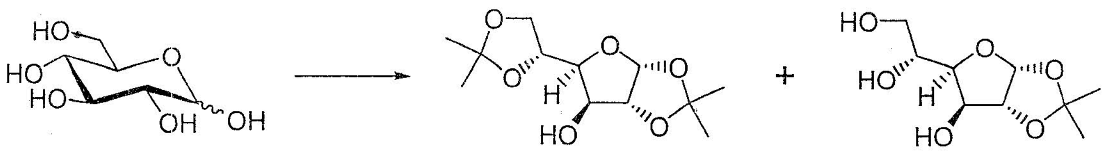
*Key words: diacetone-α-D-glucose, DAG, purification, "green" chemistry, water*

## Introduction

The constant need for broad range of homochiral compounds is one of the major impulses for development in modern organic chemistry. Advances in asymmetric synthesis are impressive; however, it requires either the use of enantiomerically pure catalyst or at least a chiral auxiliary attached to the substrate. Given its commercial availability and exceptional optical purity, diacetone-α-D-glucose **2** (DAG) has been widely used in different fields of research in organic chemistry since its discovery decades ago. It can be fairly easy synthesized from α-D-glucose, which in turn is obtainable from either starch or cellulose on a large scale.




D-glucose (**1**) diacetone-α-D-glucose (**2**) [1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose] monoacetone-α-D-glucose (**3**)

Contemporary use of DAG is demonstrated in asymmetric synthesis, where DAG is used either as an optically pure starting material [1] or a versatile chiral auxiliary [2]. The latter, for instance, has found a distinguished niche in the synthesis of enantiomerically pure sulfoxides [3]. Recent advances allow one to use dynamic kinetic resolution approach for industrial synthesis of sulfoxides [4].

The second most important aspect of DAG application is the total synthesis and drug design. Being based on biologically common sugar platform, DAG is an excellent example of a molecule coming from chiral pool. Being cheap and easily available, DAG is a promising precursor for many potential drugs, like anti-cancer [5], anti-HIV [6,7] or different di- [8] and oligosaccharides [9]. Aza- and thiosugars were developed recently, by replacing lactol ring oxygen with nitrogen [10] or sulfur [11], respectively.

Lastly, DAG is used as chelating ligand in organometallic chemistry, some metal complexes exhibit magnetic properties [12].

Though discovered long time ago, synthetic procedures towards DAG do not differ too much. In all cases glucose is suspended in anhydrous acetone and stirred with an acid, which is neutralized after reaction is complete. Most common methods of DAG synthesis are summarized in Table 1.

Table 1

Reported methods for synthesis of diacetone-α-D-glucose

| Entry | Acid | Neutralization agent | Yield | Reference |
|---|---|---|---|---|
| 1 | conc. $H_2SO_4$* | dry $NaHCO_3$ | 62 % | [13] |
| 2 | conc. $H_2SO_4$ | dry $NH_3$ | 60 % | [14] |
| 3 | conc. $H_2SO_4$ | dry $NaHCO_3$ | 65 % | [15] |
| 4 | $ZnCl_2$, $H_3PO_4$ | conc. NaOH solution | 91 % | [16] |

* 1% acetaldehyde added to increase the reaction rate.

Yields as high as 91 % (entry 4, Table 1) are reported, however the present method requires large amounts of $ZnCl_2$ and is therefore impractical. Other methods (entries 1-3, Table 1) provide the product **1** in 60...65 % yield. Acetaldehyde can be added to improve the reaction rate, but it reduces purity of the product and is not required if higher acid concentrations are used. Although one can think that any traces of water in reaction medium will force hydrolysis of isopropylidene group, we found that dry solvent is not a strict requirement – one can use not specially dried acetone without a significant decrease of product yield or purity. Moreover, concentrated sodium hydroxide solution can be used for neutralization. In this case precipitating sodium sulfate acts as *in situ* generated drying agent.

After solvent evaporation, crude DAG contains slight amounts of monoacetone-D-glucose (**3**) as a minor impurity. Moreover, the technical product is obtained as an amorphous solid. The most common way to purify DAG is its crystallization from different organic solvents: petroleum ether [15], chloroform and hexane mixture [16], ligroin [14] and other organic solvents. Since both, the synthetic procedure and the work-up of DAG are convenient and cheap, it was crucial to develop environmentally friendly purification process of that would correspond to "green chemistry" approach. To the best of our knowledge, none of such method was reported so far.

## Results and discussion

Following "green chemistry" guidelines we have developed new DAG purification method, which in is environmentally friendly. During elaboration of preparative procedure towards DAG synthesis we have observed that it is partially soluble in water. Crystallization from water is possible with limited success, because melting point of crude product is usually below 100 °C. That in turn leads to part of product melting, forming yellow oil, which complicates purification procedure and makes whole process to be unsuitable for scaling up. Both, solvent volume increase and lowering temperature results in reduced yield of crystallization.

To increase crude product solubility and to avoid technical complications mentioned above we decided to try crystallization from alcohol-water solution. In order to keep method environmentally-friendly ethanol is the solvent of choice, since it is not toxic and readily biodegradable.

Solutions with different alcohol concentration were investigated to determine DAG solubility, using pure material. The results are shown on Fig. 1.

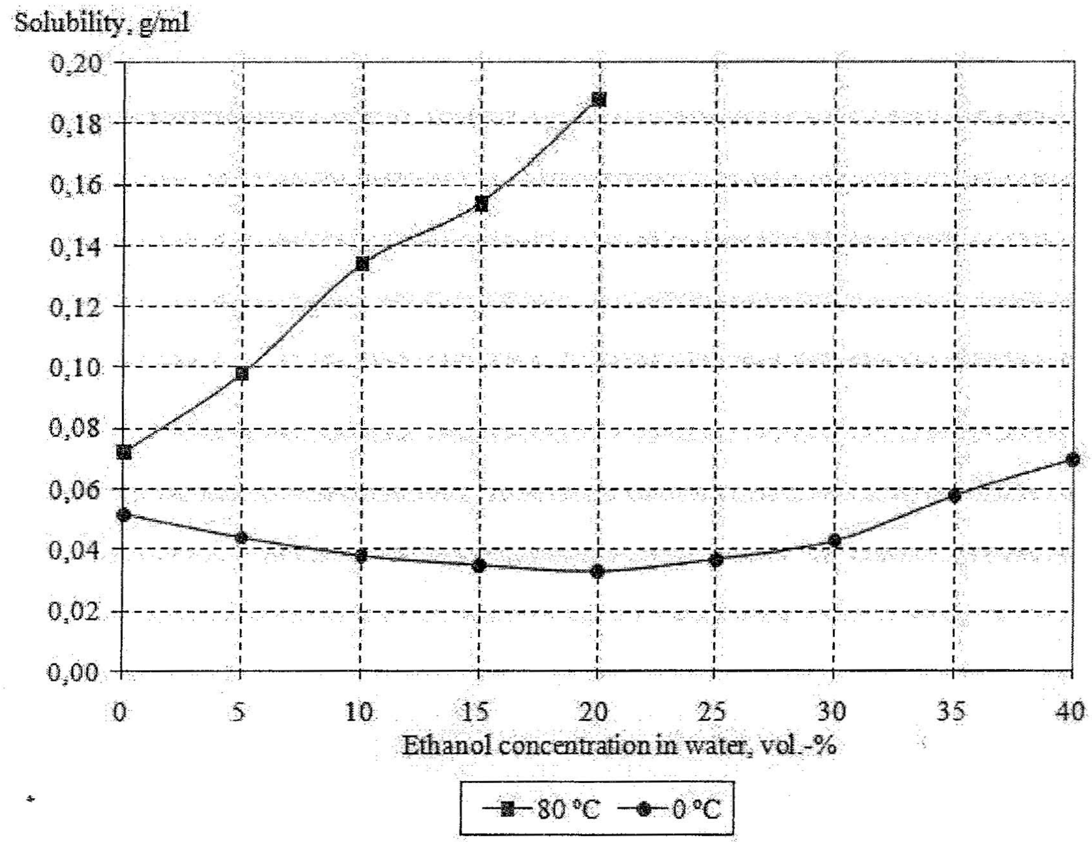



**Fig. 1.** Solubility of DAG (**2**) in water-ethanol mixtures at different temperatures

The 80 °C temperature limit was set empirically as it prevents the melting of the crude product during crystallization. On the other hand, hot crystallization mixtures with ethanol concentration above 20% (v/v) make solutions too concentrated. That eventually leads to forming of three component system (water-ethanol-DAG) which is liquid at the given temperature, therefore additional DAG readily dissolves, making it impossible to determine solubility. For this reason, higher concentrations were not specifically investigated.

Since crystallization yield correlates to the difference between material solubilities in hot and cold solutions, the best solvent composition seems to be 20 % (v/v) of ethanol in water. Corresponding DAG (**2**) concentration (0.2 g/mL) proved to be the highest, that still yields crystalline product; therefore we used it in our research.

As the next step to our investigation, we synthesized DAG (**2**) using the best preparative method [13], and continued our studies with the crude material obtained. To find the best conditions we made crystallization experiments with different solvent concentrations, measuring crystallization yields. Results show that the best conditions are still at 20 % (v/v) of ethanol in water Figure 2.

Additionally, we investigated the time of cooling needed for full precipitation of the material. For this purpose we made several experiments using conditions described above with various cooling times (Figure 3). One can see, that the majority of the material precipitates in the 2 hour period. Thus, the cooling can be reduced to 2 hours without significant loss of the crystallization yield.

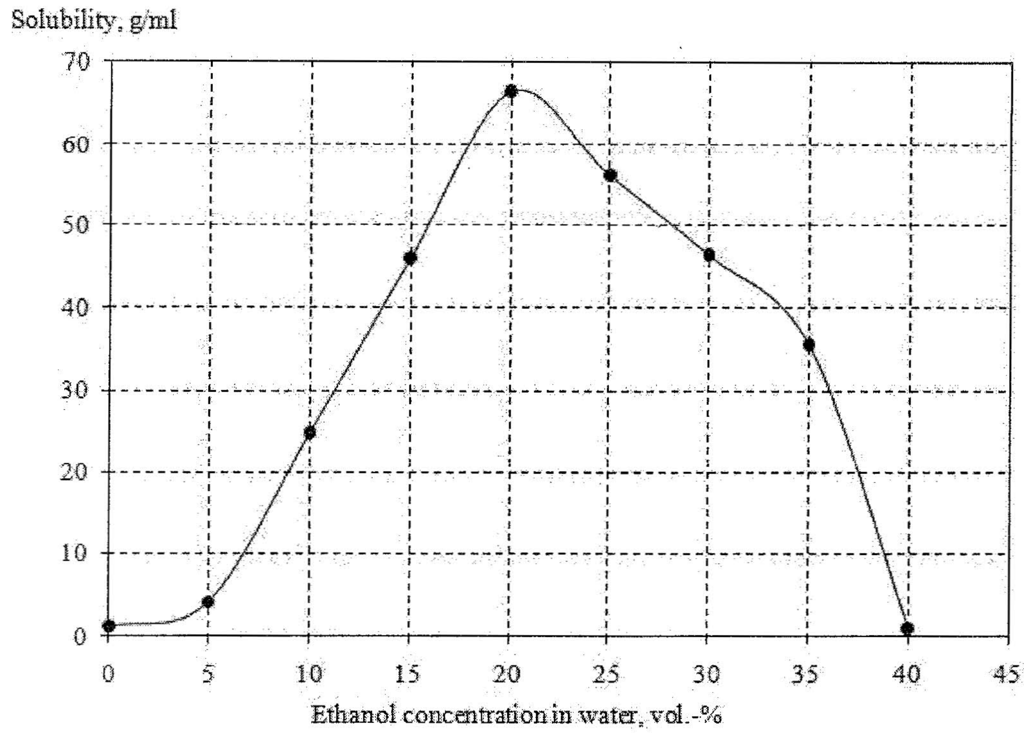



**Fig. 2.** Crystallization yields of the crude DAG (**2**)

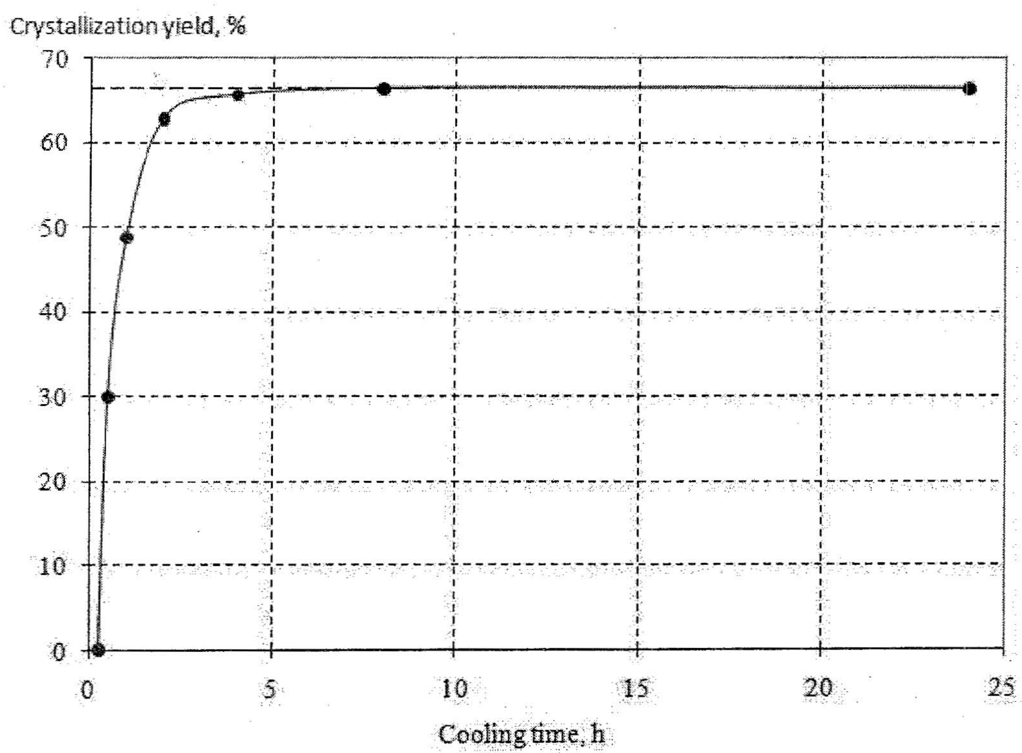



**Fig. 3.** Crystallization yield correlation with cooling time at 0..+5 °C

## Experimental

*Crystallization experiments*

Sample of commercially available DAG (5 g) was heated in oil bath (105 °C bath temperature) with appropriate solvent mixture (10 ml, Figure 2) under constant stirring. Solvent was added dropwise until solution became homogeneous. After that mixture was refluxed for 20 minutes and poured into a flask, cooled at 0°C bath with stirring in an ice for 30 minutes. The crystallization vessel was then put in a fridge (0..+5 °C) for corresponding amount of time (Figure 3). After cooling was complete, precipitate was filtered off, washed with ice-cold water (10 ml) and dried in air for 24 hours.

*Synthesis of diacetone- α-D-glucose using the new crystallization conditions*

Conc. $H_2SO_4$ (97 %, 84 mL, 1.58 mol, 1.4 equiv.) was added at 5 ... 15 °C to the suspension of α-D-glucose (100 g, 0.56 mmol, 1 equiv.) in acetone (2 L). The resulting mixture was stirred at 20 °C for 6 h, then cooled to 0 °C and neutralized with aqueus solution of NaOH (124 g in 100 mL of water) maintaining internal temperature below 10 °C. To complete the neutralization, dry $NaHCO_3$ (200 g) was added until the mixture reached pH 7..8. The mixture was filtered and the solvent evaporated, yielding crude amorphous DAG (126 g). The crude product **2** (126 g) was dissolved in a mixture of water (200 mL) and ethanol (50 mL) at 80 °C. Mixture was stirred for 20 min, then filtered hot and cooled to 0 °C and kept for 2 hours. Precipitate was filtered and dried in oven at 80 °C for 4 h. Yield: 75 g (60%).

## Conclusion

Purification of diacetone-α-D-glucose (**2**) by crystallization from water-ethanol mixtures was investigated. The optimal conditions were reached by crystallization from 20 % (v/v) ethanol/water mixture and cooling the solution at 0 °C for 2 hours before filtration yielded 60 % pure DAG. Purified product analysis showed absence of mono-protected glucose (**3**) or other major impurities, which makes the present method suitable for further syntheses. Developed purification method is cheap, convenient and both environmentally friendly, and it can be used for industrial production of DAG.

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***P. Ostrovskis, M. Turks. Videi draudzīga diaceton-α-D-glikozes attīrīšanas metode.***
*Izstrādāta metode diaceton-α-D-glikozes attīrīšanai, pārkristalizējot to no etanola-ūdens maisījuma. Atšķirībā no citur publicētām attīrīšanas metodēm tā ir videi draudzīga, kā arī saglabā augstu produkta iznākumu un kvalitāti. Ir izpētīta kristalizācijas iznākuma atkarība no šķīdinātāju kompozīcijas un dzesēšanas laika. Atrastie optimālie apstākļi ietver tehniskās DAG šķīdināšanu 20 tilp. % etanola-ūdens maisījumā pie 80 °C un dzesēšanu pie 0 °C 2 stundu laikā. Produkta iznākums ir 75%, kas nav zemāks par iznākumu citās diaceton- α-D-glikozes attīrīšanas metodēs. Produkts tiek iegūts kristāliskā formā, kas atvieglo tā tālāko izmantošanu. Izstrādāto metodi ir iespējams izmantot DAG rūpnieciskai attīrīšanai.*

***P. Ostrovskis, M. Turks. Enviromentally friendly purification of diacetone-α-D-glucose.***
*New method of diacetone-α-D-glucose crystallization from ethanol-water mixture was developed. Unlike previously reported methods it is completely environmentally friendly, while maintaining high product yield and purity. Crystallization outcome as a function from solvent composition and precipitation time was investigated. The best conditions found include dissolving crude DAG in 20% (v/v) mixture of ethanol in water at 80 °C with subsequent cooling at 0 °C for 2 hours. Purification yield using these conditions is 75%, which is comparable*

*with other diacetone-α-D-glucose purification methods. The product is obtained in easy to handle crystalline form, which makes the present method useful for up-scaling.*

***П. Островский, М. Туркс. Дружественный к окружающей среде метод очистки диацетон-α-D-глюкозы.***

*Разработан новый метод очистки диацетон-α-D-глюкозы (ДАГ) путем перекристаллизации из смеси этанол-вода. В отличие от уже известных описанный метод является безопасным для окружающей среды, сохраняя при этом высокий выход и чистоту продукта. Исследована зависимость выхода перекристаллизации от соотношения растворителей и скорости выпадения осадка. Оптимальные условия кристаллизации включают растворение технической ДАГ в 20 об. % раствора этанола в воде при 80 °C с последующим охлаждением до 0 °C в течение 2 часов. Выход продукта при оптимальных условиях достигает 75%, не ниже чем используя другие известные методы очистки. Продукт получают в виде кристаллического вещества, что облегчает его дальнейшее использование. Разработанный метод может быть использован для очистки ДАГ в промышленном производстве.*