

Direct Hydrolysis of *O,O'*-Dibenzoyltartaric Anhydride - An Alternative Method for Manufacture of the same Acid: Tartaric Acid and Its *O*-Acyl Derivatives. Part 9¹

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ABSTRACT: Efficient, direct, one-pot hydrolysis of *O,O'*-dibenzoyltartaric anhydride produced via benzoylation of tartaric acid was achieved, whereby a complete and efficient method of manufacturing *O,O'*-dibenzoyltartaric acid was developed. The process was successfully optimized by using factorial and rotatable designs. The yield was increased from 81 to 95%. The results obtained in the laboratory were then successfully implemented in the pilot-plant-scale process.

INTRODUCTION

Tartaric acid (**1**) and its acyl derivatives are very popular and attractive compounds, which have still been used in the entire field of asymmetric chemistry, allowing individual enantiomers to be obtained in different ways. They play an important role as *building blocks* in the chiral pool synthesis. They have been successfully employed in asymmetric synthesis as *chiral auxiliaries* or as *chiral ligands*, being used in numerous catalysts.^{1b,2}

Among those various applications, the use for *resolution of racemates* is the major one. Also *O,O'*-dibenzoyltartaric acid (**4**) is one of the *resolving agents* most often used for racemic mixtures of amines, as well as other compounds of a basic nature. Following the USFDA policy statements (1992), which allow marketing of new chiral drugs only in enantiomerically pure forms, there has been a growing interest in the isolation of enantiomers.³ Resolution of racemates via diastereomeric intermediates is still the major method, also applicable on an industrial scale,^{4–6} especially in pharmaceutical, food and chemical industries.

Probably due to the considerable practical importance, reports on the methods of preparation of acid **1** acyl derivatives are scattered and rather scarce. Many of them are very old and published in hard-to-access journals. Some of them are even erroneous. These reports are often in the form of patent information, brief reports in *Chemical Abstracts*, or sole notes in experimental sections. We have reviewed all of those methods up until 2008.^{1a}

Two-stage synthesis is the main classical method of producing acid **4**.^{7–18} At the first stage, corresponding anhydride **2** is prepared and then is hydrolyzed to the desired acid. The acylation of the second hydroxyl group and cyclization proceed in parallel; therefore, using only 2 equiv of acid chloride in the reaction does not result in acid **4** but instead a mixture of mono- and diacyl acids as well as corresponding anhydride **2**, from which the isolation of acid **4** is not economical.^{1c} Fortunately, the anhydride and ester bonds of anhydride **2** differ distinctly in their tendency to hydrolysis, the former undergoing it more easily than the latter. Hence, under appropriate conditions it is possible to open the anhydride ring without losing practically any acyl groups.

The use of an additional chlorinating agent, e.g. SOCl₂, is one of the most important modifications of the process resulting in a considerable decrease in the consumption of the acylating agent.¹⁷ However, a hard separable mixture of gaseous SO₂ and HCl (HCl only in the classical method) is also produced. Due to the relatively low cost of benzoyl chloride, we do not recommend this method for production of benzoyl derivatives.

RESULTS AND DISCUSSION

A two-stage process of manufacturing of **4** was implemented at the Laboratory of Technological Processes, consisting of: (1) benzoylation/dehydration of tartaric acid, to produce anhydride **2** (Scheme 1) and (2) hydrolysis of anhydride **2**, to produce the final product **4** (Scheme 2).

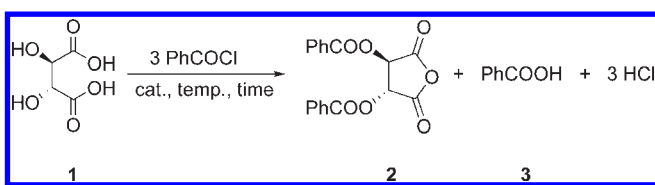
The technology was then systematically improved. The annual production was scaled up from 100 kg to 25 tons (two parallel 75-L reactors) and, upon implementation of the technology in the industry (a 1.5 m³ reactor), it exceeded 50 tons. This improvement required solving many technical problems as well as using process optimization.

There are some advantages and disadvantages of the step method. The disadvantage includes the necessity of using 3 equiv of benzoyl chloride and obtaining, as a byproduct, a mixture of anhydride **2** and benzoic acid **3** which has to be separated before hydrolysis of **2**. The system involved at the first step is quite complicated and highly corrosive. It consists of three phases: *solid* tartaric acid (**1**) and anhydride **2**, *liquid* benzoyl chloride and dissolved or melted benzoic acid (**3**), and evolving *gaseous* hydrochloride. The viscosity of the system increases as the reaction progresses. At the beginning, the mixing of 1 mol of solid **1** in 3 mol of liquid benzoyl chloride is quite efficient and easy. At the end, however, it is necessary to mix the highly viscous mixture of 1 mol of solid **2** and 1 mol of melted (at above 110 °C) acid **3** and dilute it with some inert solvent, e.g. toluene. On the other hand, the advantage of the first step is the effective separation of anhydride **2** from the benzoic acid and separation

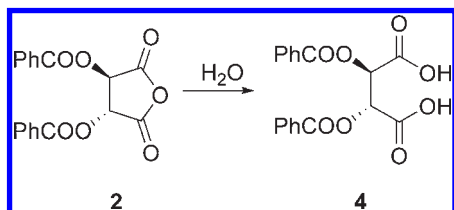
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Scheme 1. Benzoylation/dehydration of tartaric acid (1) to produce anhydride 2



Scheme 2. Hydrolysis of anhydride 2 to produce the final product 4·H₂O



from the small amount of dark impurities which pass into the toluene solution, whereas anhydride 2 is only slightly soluble. Even though the conversion of acid 1 proceeds almost quantitatively, due to some losses in filtration and drying, the isolated yield of the first step only slightly exceeds 90%.

It is crucial for hydrolysis to selectively open the anhydride 2 ring without hydrolyzing any of the benzoyl groups. It is also of key importance to obtain the form of acid 4 monohydrate that is easy to filtrate and dry. This is not a trivial task, as the melted monohydrate overcools quite easily (mp 88–89 °C) and tends to crystallize into a mass and stick to the stirrer and to the reactor walls. The advantage of the hydrolysis in water is obtaining a precipitate of the product 4, which is safe to dry. Consequently, the dryers do not have to be explosion-proof. Even though the conversion of anhydride 2 is a quantitative process, due to some subsequent hydrolysis of benzoyl groups and some losses during filtration and drying, the isolated yield of the second step was only slightly over 93%. The overall yield of the process did not exceed 81–86%.

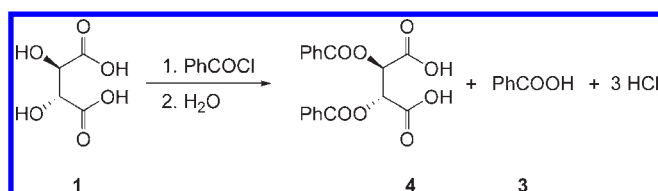
Looking for the simplest and most effective process, we decided to modify the process by performing hydrolysis of anhydride 2 immediately after its synthesis and adding toluene necessary to solve the benzoic acid, but without isolating anhydride 2 from the reaction mixture (Scheme 3).¹⁹

Such a method should significantly lower the consumption of water from the level required for it to play the role of a solvent and a reagent ($H_2O/2 = 60:1$ mol/mol) down to only (4:1). It should also eliminate the losses of anhydride 2 in the isolation stage (first step of the two-stage process), resulting in the overall yield improvement (cost reduction) of the process.

We found that the solubility of acid 4 in the toluene solution of benzoic acid 3 was significantly higher than in toluene alone (Figure 1). This might be one of the causes of the acid 4 losses in the mother liquor at the first step of the two-stage method.

Anhydride 2 and acid 4 should both be white or nearly white solids. Attaining such color is not easy, since at the benzoylation step the system is getting dark brown or even black. We found that the final color depended on the quality of toluene used. The number IZ which characterizes the color in the reaction of toluene with sulfuric acid should not exceed 0.3. A possible

Scheme 3. Obtaining *O,O'*-dibenzoyltartaric acid by a “direct hydrolysis” method



explanation of this fact is the degradation of acid 1 at high temperatures. The formation of anhydride 2 is endothermic, so the reactor is intensively heated up to the maximum reaction temperature. For safety reasons, the heating rate is limited by the efficiency of absorption of HCl—the principle of technological moderation.

We tested the effect of the maximum temperature of the synthesis of 2, z_1 , concentration, z_2 , and amount of sulphuric acid as catalyst, z_3 , on the isolated yield of 4, y_1 , the visible (Vis) absorption (at $\lambda = 600$ nm) of the post-reaction mixture (contamination with color impurities), y_2 , the HCl evolution time, y_3 , and on the benzoic acid content in 4, y_4 .

The optimization criteria were to maximize the yield of 1, y_1 , and to minimize color impurities, y_2 . To achieve this goal we decided to employ the rotatable design.²⁰ The HCl evolution time, y_3 , and the contamination of 4 with 3, y_4 , were only determined and analyzed, but not used in the optimization procedure. We expected that controlling the influence of the three variables would suffice to achieve a satisfactory yield and to obtain the product of adequate/suitable quality.

The reaction is heterogeneous because the solubility of tartaric acid and its derivatives in toluene is very low. This forced us to check for the effects of temperature and concentration, which are critical to solubility. A minimum level of concentration, z_2 , was set which would allow mixing of the suspension at the reaction temperature. The selected maximum and minimum levels of each factor are shown in Table 1. A rotatable 20-run design was used, consisting of (1) a 2-level factorial part (eight runs with three input variables at all combinations of the +1 and -1 levels), (2) a star points part (six runs with each of the three input variables at -1.682 and +1.682, while the other two were at (0) and (3) replicates at the center of the design (six runs with all three variables at 0). All of the other variables were held constant (standard conditions) (Table 2). The experiments were performed in a random order, and for each experiment all four of the response variables, y_i , were measured. Table 2 shows the design matrix along with the measured responses.

To shorten the discussion the details of statistical analysis are not presented in this paper. We present here only the selected quadratic models (without insignificant coefficients) and the most important diagrams.

Yield of 1, \hat{y}_1 (%).

$$\hat{y}_1 = 91.47 + 0.71 \cdot x_1 - 1.09 \cdot x_2 - 1.31 \cdot x_1 \cdot x_3 + 0.59 \cdot x_1^2 - 0.40 \cdot x_2^2 - 0.95 \cdot x_3^2$$

The diagram of the dependence of yield 4, \hat{y}_1 , on the concentration (amount of toluene used for benzoylation), x_2 , and the amount of sulfuric acid, x_3 , at a constant optimal temperature, $x_1 = 1.682$, (calculated with the MS Solver) is shown in Figure 2.

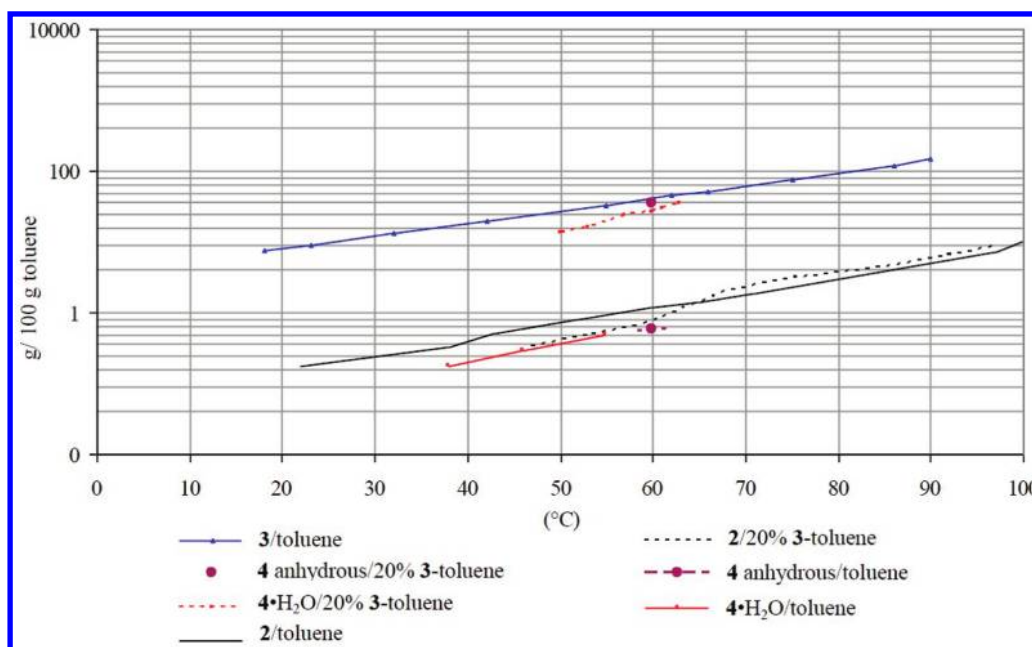


Figure 1. Solubility of reaction components in toluene and in the toluene solution of 20% of 3.

Table 1. Factorial 2^3 and rotatable designs: variables at maximum and minimum levels

z_i	natural variable	(-1.682)	(-1)	(0)	(+1)	(+1.682)
z_1	max. temperature (°C)	98.2	105	115	125	131.8
z_2	toluene amount (g/g of 1)	0.48	0.65	0.90	1.15	1.32
z_3	sulfuric acid amount (mg/g of 1)	8.2	15	25	35	41.8

Vis absorbance, \hat{y}_2 .

$$\hat{y}_2 = 0.277 + 0.037 \cdot x_1 + 0.117 \cdot x_2 + 0.040 \cdot x_3$$

The diagram of the dependence of Vis absorbance, \hat{y}_2 , on the concentration (amount of toluene used for benzoylation), x_2 , and the amount of sulfuric acid, x_3 , at a constant optimal temperature, $x_1 = 1.682$, (calculated with the MS Solver) is shown at Figure 3.

HCl evolution time, \hat{y}_3 (min).

$$\hat{y}_3 = 135.3 - 33.9 \cdot x_1 - 5.5 \cdot x_1^2 - 17.8 \cdot x_2^2 - 19.6 \cdot x_3^2$$

The diagram of the dependence of HCl evolution time, \hat{y}_3 , on the concentration (amount of toluene used for benzoylation), x_2 , and the amount of sulfuric acid, x_3 , at a constant optimal temperature, $x_1 = 1.682$ (calculated with the MS Solver) is shown at Figure 4.

Contamination of 4 with 3, \hat{y}_4 (%).

$$\hat{y}_4 = 1.54 - 0.35 \cdot x_1 - 0.34 \cdot x_1 \cdot x_3 + 0.65 \cdot x_1^2 - 0.40 \cdot x_2^2 - 0.25 \cdot x_3^2$$

The diagram of the dependence of the contamination of 4 with 3, \hat{y}_4 , on the concentration (the amount of toluene used for benzoylation), x_2 , and the amount of sulfuric acid, x_3 , at a constant optimal temperature, $x_1 = 1.682$ (calculated with the MS Solver) is shown in Figure 5.

Summary of the Laboratory-Scale Experiments. The influence of the maximum reaction temperature, x_1 , the amount of toluene, x_2 , and sulfuric(VI) acid (as a catalyst), x_3 , used for benzoylation, on the yield of acid 4, y_1 , produced via the direct one-pot hydrolysis of *O,O'*-dibenzoyltartaric anhydride (2) formed through the benzoylation of tartaric acid (1) was investigated. Using the estimated function, \hat{y}_1 , it was found that, within the design limits, the yield, \hat{y}_1 , decreased with increasing amount of toluene, x_2 , and of the catalyst, x_3 , and increased with increasing temperature, x_1 . The upper range of the observed yield of 4 was from 87.6 to 95.3%.

Due to the positive influence of temperature on the process yield, y_1 , the optimal temperature within the design limits, was found to be $z_1 = 131.8$ °C, corresponding to the star point $x_1 = 1.682$. The optimal conditions within the design limits, as calculated by the MS Solver, were $x_2 = -0.4$ and $x_3 = -1.3$; $\hat{y}_1 = 96.1\%$. From the diagram, the optimal ranges may be estimated x_2 between -0.8 and 0 , and x_3 between -1.6 and -1.0 (Figure 2).

In spite of the essential differences between the measured Vis absorption response, y_2 , and the estimated one, \hat{y}_2 , a minimum of \hat{y}_2 is visible in the area near to the maximal yield, \hat{y}_1 (Figure 3). Small amounts of toluene and of sulfuric acid, x_2 , ($x_3 < 0$), are advantageous for the quality of the product (the lower Vis absorbance, \hat{y}_2 , the fewer color impurities). The minimal concentration of these impurities in one-pot direct hydrolysis is especially important, because the water present decreases their solubility in toluene. These impurities cause the color of the final product 4 to become darker grey than acceptable. Contrarily, in the two-stages process, the impurities are adequately soluble in the toluene mother liqueur (which is dark), so the isolated anhydride 2 can be purified before hydrolysis.

The dependence of HCl evolution time, \hat{y}_3 , on the amounts of toluene, x_2 , and of sulfuric acid, x_3 , used for benzoylation, has a maximum, $\hat{y}_3 = 7.8$ min, at $x_2 = 0.7$ and at $x_3 = -0.3$ (Figure 4). Decreasing the amount of toluene, x_2 , and that of sulfuric acid, x_3 , towards the conditions optimal for the process yield, \hat{y}_1 , shortens

Table 2. Factorial 2³ and rotatable designs: experimental matrix^a and results^b

trial no.	coded variables			yield of 4		Vis absorbance ^c		HCl evolution time		contamination of 4 with 3	
	x_1	x_2	x_3	resp y_1 (%)	calcd \hat{y}_1	resp y_2	calcd \hat{y}_2	resp y_3 (min)	calcd \hat{y}_3	resp y_4 (%)	calcd \hat{y}_4
1	-1	-1	-1	91.0	89.9	0.1569	0.226	110	116	1.63	1.54
2	+1	-1	-1	94.0	93.6	0.1550	0.268	40	38	1.29	1.70
3	-1	+1	-1	88.7	88.2	0.3261	0.310	160	171	1.23	1.46
4	+1	+1	-1	91.4	92.5	0.3110	0.386	110	98	1.17	1.26
5	-1	-1	+1	94.4	92.6	0.1053	0.049	80	99	2.05	2.03
6	+1	-1	+1	91.2	91.1	0.2202	0.255	40	37	1.00	0.84
7	-1	+1	+1	89.6	89.4	0.3712	0.277	110	119	2.91	2.57
8	+1	+1	+1	88.0	88.5	0.5687	0.517	60	61	0.86	1.02
9	0	0	0	90.4	91.5	0.1693	0.171	100	135	0.95	1.54
10	0	0	0	92.1	91.5	0.1677	0.171	180	135	1.02	1.54
11	0	0	0	91.5	91.5	0.1713	0.171	120	135	1.63	1.54
12	0	0	0	91.5	91.5	0.1711	0.171	120	135	1.74	1.54
13	0	0	0	91.5	91.5	0.1702	0.171	100	135	1.94	1.54
14	0	0	0	92.0	91.5	0.1744	0.171	190	135	1.97	1.54
15	-1.682	0	0	90.1	92.0	0.0911	0.158	200	177	3.79	3.96
16	+1.682	0	0	95.3	94.3	0.4884	0.396	50	63	3.06	2.80
17	0	-1.682	0	90.5	92.2	0.2541	0.168	60	52	0.43	0.39
18	0	+1.682	0	89.3	88.5	0.3978	0.459	120	118	0.52	0.47
19	0	0	-1.682	89.1	89.3	0.4011	0.267	100	102	1.08	0.74
20	0	0	+1.682	87.6	88.3	0.1198	0.228	70	58	0.70	0.95

^a Standard conditions: all experiments were performed using the same raw materials (diameter of 1: 0.2–0.8 mm); at a scale of 31.5 g (0.21 mol) of 1, PhCOCl/1 3.0 mol/mol; rate of stirring: benzoylation 250 min⁻¹, hydrolysis and crystallization 500 min⁻¹; post-reaction time 20 min; toluene for hydrolysis 3.8 g_{Tol}/g₁; water for hydrolysis 4 mol_{H₂O}/mol₁; hydrolysis temperature and time 92 °C, 30 min; toluene for crystallization 6.34 g_{Tol}/g₁; crystallization time ~2 h; crystallization temperature 72–27 °C; filtration temperature 27 °C; washing with toluene 2.1 g_{Tol}/g₁ and with water 2 × 3.2 g_{H₂O}/g₁; drying 60 °C, 5 kPa, 2 h. ^b All \hat{y}_i have been calculated from the quadratic model. ^c $\lambda = 600$ nm.

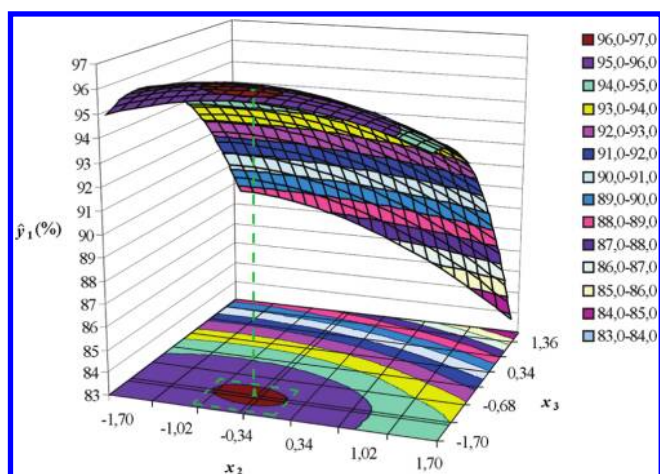


Figure 2. Dependence of yield 4, \hat{y}_1 , on the amount of toluene, x_2 , and of sulfuric acid, x_3 , used for benzoylation; $x_1 = 1.682$.

the HCl evolution time, \hat{y}_3 , and increases the reaction rate. Because of the adequately high HCl evolution rate, the absorption of HCl has to be very efficient. For safety reasons, though, one must be very careful here. Our absorption unit was so efficient that the HCl absorption rate was never a bottleneck in the experiment, even though the reaction system warmup time was at a minimum (the reactor was just plunged into the bath at the reaction temperature).

It seemed that it would be difficult to observe the influence of the conditions of synthesis of 2 on the contents of impurities in

final product 4, as measured at the end of the whole process. However, unexpectedly, a good model was obtained for the contamination of product 4 with acid 3, \hat{y}_4 . The behavior of the diagram of \hat{y}_4 is very similar to that of \hat{y}_1 , with a maximum (the worst result), $\hat{y}_4 = 3.10\%$, at $x_2 = -0.4$ and at $x_3 = -1.2$ (Figure 5).

The two responses (HCl evolution time, y_2 , and Vis absorption, y_3) depend directly on the first-stage conditions (temperature, and the amounts of toluene and sulfuric acid), but the other two (the yield, y_1 , and product contamination, y_4) depend additionally on the filtration, washing, and drying of 4. Despite the standardization of the second stage, the results of the latter two responses might have higher variability.

Maximizing the process yield, \hat{y}_1 , leads to the following optimal conditions:

- maximal temperature $x_1 = +1$ to 1.7, $z_1 = 125$ –132 °C
- amount of toluene $x_2 = -0.8$ to 0, $z_2 = 0.7$ –0.9 g_{Tol}/g₁
- amount of catalyst $x_3 = -1.6$ to -1.0 , $z_3 = 9$ –15 mg_{SA}/g₁

The standard conditions of the second process step and the final workup are as follows:

- hydrolysis - toluene: 3.8 g_{Tol}/g₁ (to solve the formed benzoic acid); water: 4 mol_{H₂O}/mol₁
- crystallization - toluene: 6.8 g_{Tol}/g₁, time: not less than 2 h with final temperature 27 °C (the shorter the time, the higher the content of acid 3 in the product 4); washing of 4 on the filter: once with toluene, 1 × 2.1 g_{Tol}/g₁ and twice with water, 2 × 3.2 g_{H₂O}/g₁, each time with stirring

The final product, 4 · H₂O, was obtained with a high yield, $y_1 = 93\%$, and with an adequate purity (the proper shade of whiteness).

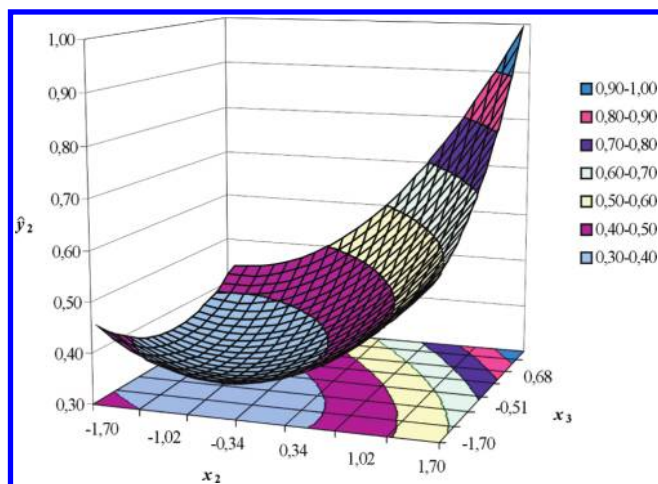


Figure 3. Dependence of Vis absorbance, \hat{y}_2 , on the amount of toluene, x_2 , and of sulfuric acid, x_3 , used for benzylation; $x_1 = 1.682$.

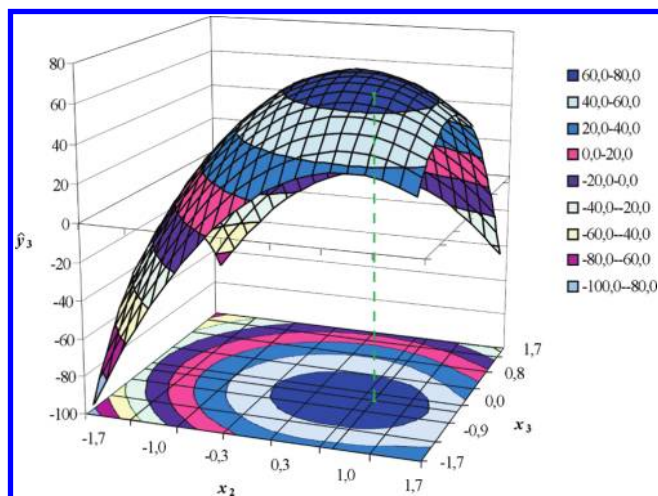


Figure 4. Dependence of HCl evolution time, \hat{y}_3 , on the amount of toluene, x_2 , and of sulfuric acid, x_3 , used for benzylation; $x_1 = 1.682$.

Scaling Up of the Process. The optimal conditions determined in the laboratory tests were used as a guideline for experiments in an 80-L pilot-plant reactor. The warming-up rate of this reactor is limited by the efficiency of heating system. The optimal temperature should be reached as quickly as possible, but the rate of increasing temperature has to be strictly controlled due to the hazardous evolution of HCl and the efficiency of its absorption. It is especially important not to exceed the critical HCl evolution rate at the beginning of the reaction.

The aim of the work was to scale up the process of manufacturing acid **4** via the “direct hydrolysis method” under the optimal conditions as determined previously. Moreover, all the technical problems had to be resolved, and the yield and quality of product **4** had to be determined.

The technological process shown at the block diagram (Figure 6) was carried out in an installation consisting of the following major parts:

- a raw materials feed unit (a toluene feeder, and a benzoyl chloride metering pump)
- a unit for the synthesis and hydrolysis of **2** (an 80-L reactor with an anchor stirrer)

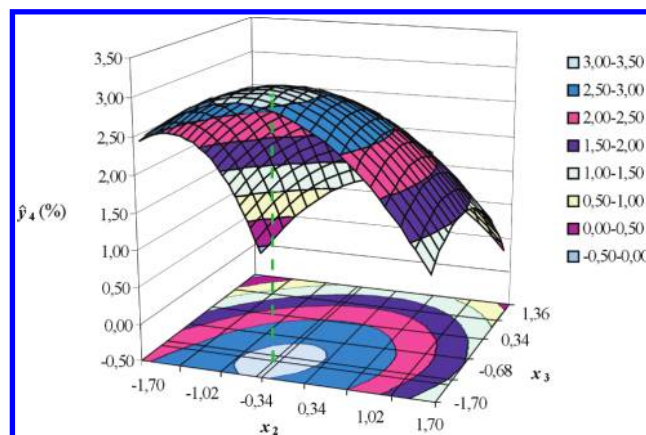


Figure 5. Dependence of the contamination of **4** with **3**, \hat{y}_4 , on the amount of toluene, x_2 , and of sulfuric acid, x_3 , used for benzylation; $x_1 = 1.682$.

- an HCl absorption assembly
- a unit for crystallization of **4** (a 100-L reactor with a turbine stirrer, and a porcelain filter)
- a neutralization unit (a 100-L reactor and a tank for mother liquors)
- shelf drier

The process was carried out as described in the Experimental Section. The process variables and their limits were identical to those in the laboratory experiment. The synthesis of anhydride **2** was carried out with a minimal amount of toluene, z_2 , 0.7 kg_{Tol}/kg₁ and, for safety reasons, with a slightly smaller amount of catalyst, z_3 , 7.5 mg_{SA}/g₁, compared to the optimal laboratory value (min. 9 mg_{SA}/g₁). For safety reasons (to control the HCl evolution rate), the temperature was increased for a duration of 2.5–3 h until it had reached the final value of 130 °C. The hydrolysis of anhydride **2** was carried out with a water excess 2 times the stoichiometric amount (0.5 kg_{H₂O}/kg₁; 4 mol_{H₂O}/mol₁), after adding toluene in the amount of (3.8 kg_{Tol}/kg₁), as in the laboratory experiments.

Due to possible unexpected scale-up effects, the crystallization conditions were verified in the following region:

- crystallization time - 30–120 min (temperature decrease rate $-1-0.25^\circ/\text{min}$, 55–25 °C, seeding at 55 °C)
- washing of product **4** with toluene - 1.6–3.2 kg_{Tol}/kg₁ (1–2 portions of 12.5 kg, each)
- washing of product **4** with water - 1.6–6.4 kg_{H₂O}/kg₁ (1–4 portions of 12.5 kg, each)

The product **4**·H₂O (93% yield) was of adequate quality, but it looked slightly different from the one crystallized from water. It was finer-grained, similar to talc powder, with almost white (slightly grey or yellow) color. The filtration was easy; however, a small amount of the powdery precipitate did pass through the filter cloth. Both the appearance and contamination with benzoic acid depend on the crystallization conditions. To obtain a pure product (the content of **3** <0.32%), it was necessary to cool the system down from 55 to 25 °C with intensive stirring for 2 h. Washing with one portion of toluene was sufficient to get rid of acid **3**; however, washing with two portions of water was necessary to obtain the adequate color (a slightly greyish tint was caused by color impurities formed during the synthesis of anhydride **2**). Some residual HCl (if not sufficiently washed out with water) caused the formation of yellow spots during drying or prolonged storage. Due to the corrosive nature of the system

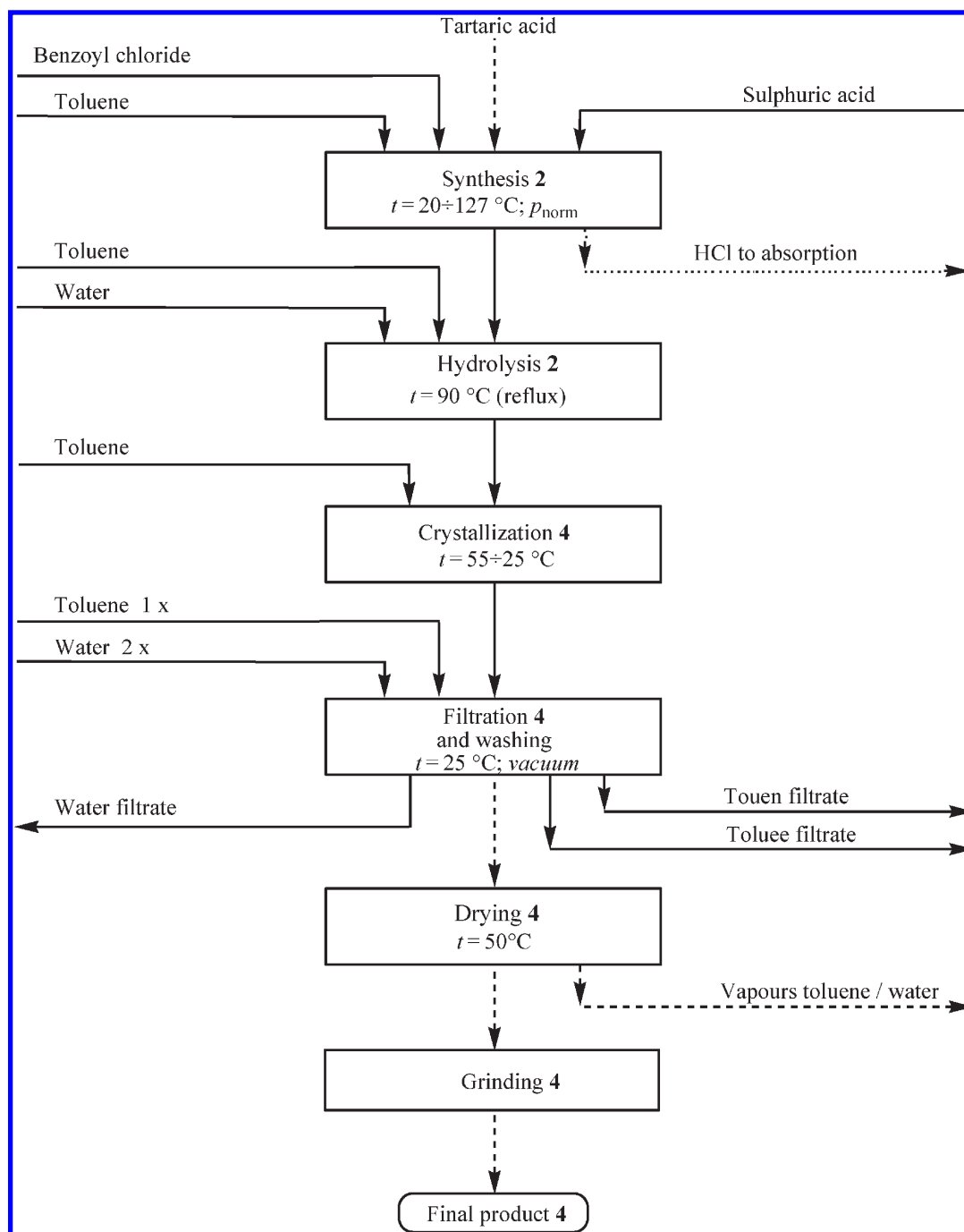


Figure 6. Block diagram of the acid 4 manufacturing process by the “direct hydrolysis method” at a pilot-plant scale.

caused by the addition of water, using the typical stainless steel as a constructional material for the filter is excluded.

Seeking the best technical solution, we constructed a laboratory filter dryer model. A batch of wet 4 precipitate after filtration was dried in this filter dryer under vacuum with a small air flow, without agitation, for 6.5 h. The temperatures were as follows: $60 \text{ }^\circ\text{C}$ in the heating jacket, $56 \text{ }^\circ\text{C}$ near the wall, and $25 \text{ }^\circ\text{C}$ in the middle of the filter dryer interior. We found that the wet precipitate of $4 \cdot \text{H}_2\text{O}$ turned into paste more easily at elevated temperatures; thus, during drying, the agitation and/or rubbing of the product should be avoided, or done very carefully.

It was found that after filtration 28% of the toluene remained in the precipitate, and after two additional water washes 17% of the toluene was still present in the precipitate of product 4. Due to the hazard of explosion and the nature of the $4 \cdot \text{H}_2\text{O}$ precipitate (forming paste when rubbed, melting and forming hard glassy particles), the selection of an appropriate EX dryer, e.g. a filter dryer, is quite difficult, and such a device is rather expensive.

CONCLUSIONS

We have developed a method for the direct one-pot hydrolysis of *O,O'*-dibenzoyltartaric anhydride (2) formed via benzoylation

of tartaric acid (1), which provides a complete and efficient technology of manufacturing of *O,O'*-dibenzoyltartaric acid monohydrate, $4 \cdot \text{H}_2\text{O}$. The process was successfully optimized by using factorial and rotatable designs. The yield was increased from 81 to 95%. The results obtained in the laboratory tests were then successfully implemented at a pilot-plant scale (93% yield).

The high yield is the most important advantage of the new method. It results from carrying out both the benzylation/dehydration reaction of acid 1 and the hydrolysis of thus-formed anhydride 2 one right after the other in a one-pot manner. However, the concentration of color impurities (formed by reaction with benzoyl chloride) has to be kept at its lowest level, a hindrance to the effective purification of anhydride 2 in the two-stage method (the color impurities are readily soluble in toluene); however, it is more difficult to get rid of these impurities (they are less soluble in the water–toluene emulsion), and thus, a very effective stirrer will be necessary. Finally, the overall water consumption is approximately 3 times lower compared to the two-stage process. On the other hand, the amount of toluene in the loop increased by 25% due to the lower concentration (more toluene) during crystallization, which was necessary to prevent the increase of the solubility of acid 4 caused by the presence of acid 3.

When implementing the “direct hydrolysis method” at an industrial scale it is vital to remember that the system is highly corrosive (due to the hydrochloric acid). Using toluene may pose explosion hazards (especially during the drying of the final product, $4 \cdot \text{H}_2\text{O}$), therefore explosion-proof equipment is essential.

EXPERIMENTAL SECTION

Commercially available solvents and reagents were used without further purification. UV spectra (to determine the color impurities) were obtained using a UV–Vis–NIR Cary 2315 Varian spectrophotometer. The HCl concentration in the absorber was determined continuously using an Elmetron CP-315 M pH-meter/potentiometer with a combined pH electrode and MT-100 temperature sensor. The benzoic acid (3) content in acid 4 was determined by HPLC (using external calibration) performed with an Agilent Technologies HP 1100 chromatograph on a LiChrospher 100 RP-18 column (250 mm \times 4 mm \times 5 μm); the eluent (2.0 g NaClO_4 /10 mL triethylamine/250 mL CH_3CN filed with water to 1000 mL; a constant pH = 3, stabilized with 85% H_3PO_4); flow rate 0.8–0.9 mL/min, a UV–Vis detector (λ = 200–700 nm). The samples were dissolved in the eluent.

Synthesis of *O,O'*-Dibenzoyltartaric Acid (4): The Representative Laboratory Procedure. 1 (31.5 g; 0.21 mol) was added to the mixture of benzoyl chloride (88.5 g; 0.63 mol) and the established amounts of H_2SO_4 and toluene (Table 1, 2). The mixture was stirred at 250 min^{-1} and rapidly heated up to the predetermined temperature (Table 2) (the 250-mL reaction flask was immersed into the oil bath); the intensive evolution of HCl was observed. Twenty minutes after the evolution had ceased, toluene (109.2 g minus the amount determined from Tables 1 and 2) was added, the mixture was cooled down to 20 $^\circ\text{C}$, and a sample of the clear solution was taken for Vis analysis (for color impurities). Next, the mixture was heated up to 92 $^\circ\text{C}$ while being stirred at 500 min^{-1} , and water (15.2 g; 0.84 mol) was quickly poured in drops to the postbenzylation/dehydration mixture; the resulting mixture was refluxed for 30 min, and then toluene (90.4 g) was added. The crystallization of 3 followed with intensive stirring and cooling down from 72 to

27 $^\circ\text{C}$ for a duration of 2 h. After filtration, the raw product was washed first with toluene (75 mL) and then twice with water (2×100 mL). After drying at 60 $^\circ\text{C}$, 5 kPa for 2 h, the yield of $4 \cdot \text{H}_2\text{O}$ and the contamination with benzoic acid were determined.

Synthesis of *O,O'*-Dibenzoyltartaric Acid (4): The Pilot-Plant Procedure. 1 (8.0 kg; 53 mol) was added to the mixture of benzoyl chloride (22.4 kg; 159 mol), H_2SO_4 (60 g), and toluene (5.6 kg; 6.5 L) in an 80-L reactor with an anchor stirrer. The mixture was stirred, and the temperature was raised rapidly (in 30 min) to 90 $^\circ\text{C}$, then slowly (in 1–1.5 h) to approximately 106 $^\circ\text{C}$, with the intensive evolution of HCl; then, after the evolution had ceased, again rapidly to 125–130 $^\circ\text{C}$ (in 20 min), to melt/dissolve the formed benzoic acid (mp 122 $^\circ\text{C}$). After 90 min, toluene (24.4 kg; 28.4 L) was added, and water (3.8 kg; 212 mol) was quickly poured in drops to the postbenzylation/dehydration mixture. The resulting mixture was refluxed at 89–92 $^\circ\text{C}$ for 30 min, and then transferred to the 100-L crystallizer with the toluene (24.4 kg; 28.4 L) with some seeding crystals of acid 4. The crystallization of 4 was followed with intensive stirring and cooling down from 55 to 27 $^\circ\text{C}$ for a duration of 2 h. After filtration, the raw product was washed first with toluene (15.5 kg; 18 L) and then two times with water (2×12.5 L). After drying in the vacuum filter for 12 h at room temperature, and then in the shelf dryer for 12 h at 50 $^\circ\text{C}$, 18.5 kg of $4 \cdot \text{H}_2\text{O}$ was obtained (a yield of 92.7%).

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■ NOTE ADDED AFTER ASAP PUBLICATION

This paper was published on the Web on Feb 28, 2011, with an error in the equation for \hat{y}_1 . The corrected version was reposted on Mar 4, 2011.