Organic Process Research & Development **1999**, *3*, 38–43

Optimisation of the Preparation and Isolation of 5-Amino-2,4,6-triiodoisophthalic Acid Dichloride

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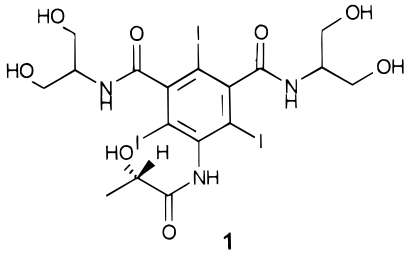
Abstract:
A scaleable process for the chlorination of 5-amino-2,4,6-triiodoisophthalic acid to the corresponding acid chloride, a building block for the synthesis of iodinated X-ray contrast agents, has been developed. Two dimeric byproducts have been isolated and assigned structures consistent with an amide and an anhydride. Hydrolysis of the N-sulfinyl intermediate and simultaneous crystallisation of the phthalic acid chloride have been optimised by applying fractional factorial design.

Introduction

The 5-amino-2,4,6-triiodoisophthalic moiety is the basic backbone responsible for the contrasting capability of many water-soluble, nonionic iodinated X-ray contrast agents[1] for imaging soft tissues, such as Iopamidol[2] (**1**), Iohexol[3] (**2**), and Ioversol[4] (**3**). Consequently, several examples of the synthesis of the key intermediate building block 5-amino-2,4,6-triiodoisophthalic acid chloride (**5**) have been reported.[5−12] Conversion of 5-amino-2,4,6-triiodoisophthalic acid (**4**) to the corresponding acid chloride **5** is usually carried out using thionyl chloride as the chlorinating agent.

Most of the procedures described for the chlorination of **4** either have a low space-time yield or are difficult to scale-up because of safety issues, generation of unacceptably high levels of impurities, and problems associated with isolation.

After we had encountered problems during scale-up of our standard reaction conditions (see Experimental Section) due to poor crystallisation and high moisture content of the isolated crystals, we embarked on an extensive study to find the optimal conditions necessary for a robust process to produce ton quantities of 5-amino-2,4,6-triiodoisophthalic acid dichloride.



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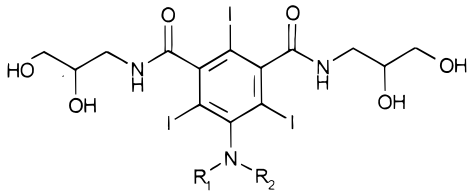
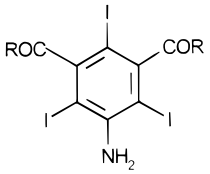


2: R_1=Acetyl, R_2=2,3-dihydroxypropyl
3: R_1=Hydroxyacetyl, R_2=2-hydroxyethyl



4: R=OH
5: R=Cl

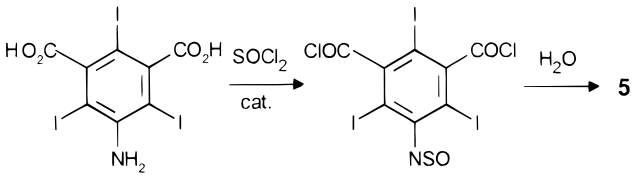
Optimisation Studies

To achieve acceptable reaction rates and to drive the reaction to completion, the formation of the acid chloride **5** reported in the literature is generally carried out at elevated temperatures and in the presence of a catalyst such as DMF.[7] The reaction has been performed in an excess of thionyl chloride, acting both as a reagent and as the solvent,[5−7] but recent patents describe the use of cosolvents to render the reaction more controllable and to avoid the use of an excess of thionyl chloride.[8−10] In earlier patents, Mallinckrodt researchers describe the use of ethyl acetate,[11] but this gives low yields and partial breakdown of the solvent. Other esters, e.g., isopropyl acetate, lead to similar problems. Chlorinated solvents such as methylene chloride[10] are not acceptable for environmental reasons and, moreover, result into prolonged reaction times and give the product as a finely divided

(1) *Radiocontrast Agents, Handbook of Experimental Pharmacology*, Vol. 73; Sovak, M. Ed.; Springer-Verlag: Berlin 1993.
(2) (a) Felder, E. *Invest. Radiol.* **1984**, *19*, S164. (b) Felder, E.; Grandi, M.; Pitre, D.; Vittadini, G. *Anal. Profiles Drug Subst.* **1988**, *17*, 115
(3) (a) Haria, M.; Brogden, R. N. *CNS Drugs* **1997**, *7*, 229. (b) Haavaldsen, J.; Nordal, V.; Kelly, M. *Acta Pharm. Suec.* **1983**, *20*, 219.
(4) Thesen, R. *Pharm. Ztg.* **1992**, *137*, 36.
(5) Smith, K. R. Ger. Offen. DE 2710730, 1977; Belg. Pat. BE 852418, 1977 (to Mallinckrodt).
(6) For example, see: Felder, E.; Pitre, D. Ger. Offen. DE 2547789, 1976 (to Savac). Felder, E.; Vitale, R. S.; Pitre, D. E. U.S. Patent 4001323, 1977 (to Savac). Felder, E.; Pitre, D. Eur. Pat. Appl. EP 23992, 1981 (to Bracco).
(7) Dimo, I.; Bonnemain, B.; Hardouin, M. J. C.; Lautrou, J. (S. A., Fr.). Eur. Pat. Appl. EP 118347, 1984 (to Guerbet).
(8) Mauro, M.; Viscardi, C. F.; Gagna, M. PCT Int. Appl. WO 96/37459, 1996 (to Fructamine).
(9) Villa, M.; Pozzoli, C.; Russo, L.; Costaldi, G. PCT Int. Appl. WO 96/36590, 1996 (to Zambon).
(10) Cannata, V.; Velgi, C.; Barreca, G. PCT Int. Appl. WO 96/16927, 1996 (to Zambon).
(11) For example, see: Kneller, M. T.; Lin, Y.; Wheatley, J. PCT Int. Appl. WO 94/05337, 1994 (to Mallinkrodt). Lin, Y. Eur. Pat. Appl. EP 83964, 1983 (to Mallinckrodt).
(12) Pillai, K. M. R.; Diamantidis, G.; Duncan, L.; Ranganathan, R. S. *J. Org. Chem.* **1994**, *59*, 1344.

10.1021/op980055+ CCC: $18.00
Published on Web 12/11/1998

Scheme 1



4 **6**

precipitate, which is difficult to isolate. A patent by Fructamine SPA describes the use of a range of aliphatic and aromatic hydrocarbons.[8] In our hands, however, the use of toluene still requires an excess of thionyl chloride, which is difficult to recycle as a mixture with toluene.

Although the patents cited above[8−10] mention the danger of using neat thionyl chloride, in our experience it is by far the best option. Addition of thionyl chloride to the dicarboxylic acid **4**, even when not completely dry, and subsequent heating do not lead to unacceptable exothermic or runaway behaviour under any conditions evaluated. The reaction is mildly endothermic, and in the presence of a catalyst such as DMF, heating above 50 °C is required in order to achieve an acceptable reaction rate. After the reaction has gone to completion, excess thionyl chloride can be distilled off under reduced pressure and reused in subsequent batches. The remaining traces of thionyl chloride in the crude product can be removed efficiently by dissolving the residue in toluene and subsequently distilling the toluene/thionyl chloride mixture under reduced pressure.

In the literature, several catalysts are described for the chlorination of **4**, including DMF,[7] *N*-methylmorpholine,[8] tertiary amines,[8] and quaternary ammonium salts.[9] Although DMF normally is a common catalyst for this type of reaction, we have encountered the formation of a precipitate and a decrease in reaction rate near the end of the reaction. DMF-catalysed reactions can be driven to completion only by increasing the reaction temperature to 80−90 °C for several hours, leading to unacceptably high levels of byproducts. Apparently, the catalyst decomposes, probably either by forming insoluble, unidentified complexes with the iodinated intermediates in the reaction or by other decomposition routes, as have been suggested recently.[13] Moreover, the use of DMF as catalyst with thionyl chloride has recently been questioned on safety grounds owing to the formation of highly toxic byproducts.[13] Therefore, several catalysts, not covered by patents, have been tested, among which were *N*-methylpyrrolidone and tetramethylurea. Both give catalytic activities similar to that of DMF, but no precipitation or deactivation during the reaction has been observed.

During chlorination of the carboxylic acid groups, the amino functionality in **4**, which is extremely difficult to protonate, also reacts quickly with thionyl chloride, giving the N-sulfinyl compound **6** as the principal product at the end of the reaction (Scheme 1).[8] This intermediate **6** is conveniently isolated by concentration of the reaction mixture or direct crystallisation in an aprotic organic solvent, as described by Mallinckrodt.[11] Therefore, isolation of **5** requires a hydrolysis step during workup of the reaction mixture. This can be achieved by washing a solution of the crude N-sulfinyl compound **6** in a suitable organic solvent with an aqueous phase for an extended period of time.[5,6] The resulting hydrolysed product **5** also has to dissolve reasonably well in the organic solvent used, making subsequent crystallisation in the same solvent difficult to perform without any losses. A solvent switch has been applied in these cases by others,[5,6] making the process more elaborate. An attractive alternative has been worked out by us to perform the hydrolysis and precipitation/crystallisation in one step.

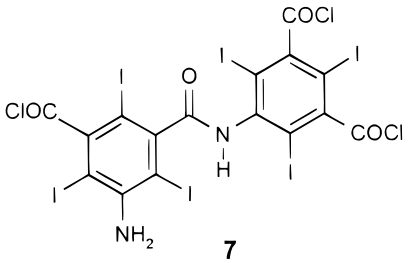
In most solvents, the N-sulfinyl compound **6** is more soluble than the desired product **5**, and addition of water to a solution of the N-sulfinyl compound **6** in a solvent in which the product is not very soluble should give precipitation of **5**. Both product **5** and N-sulfinyl compound **6** are very poorly soluble in water, and (partial) precipitation of **5** during hydrolysis of **6** will inevitably lead to inclusion of **6** in the precipitate of **5** and hence to incomplete hydrolysis of the N-sulfinyl group. As a consequence, some impurity levels of **6** have always been observed in the final product. Only use of large volumes of organic cosolvent, which keeps the product **5** in solution until hydrolysis of **6** is complete, can avoid inclusion of impurity **6** in the product. This, however, is not attractive from an economic point of view. The presence of **6** as a major impurity in **5** is often not mentioned in the literature[14] and has probably not been noticed in previous work, since **6** is hydrolysed to **5** during reversed-phase HPLC analysis of the product. Therefore, in addition to this standard HPLC method, a water-free, normal-phase method was employed to determine the level of N-sulfinyl compound. In this way, evidence has been found that the hydrolysis of **6** with concomitant crystallisation/precipitation of **5** with just water leads to unacceptable levels (above 1%) of **6** in the final product. To solve this, a search for a suitable cosolvent with an optimal balance between solubility of **6** and insolubility of **5** was initiated. From previous large-scale runs, we have learned the vital importance of a good crystallisation procedure leading to easy centrifugation of the crystals. This has proven to be relevant not only for a reduction in run cycle time but also for a low moisture content in the product. Although the phthalic acid chloride **5** is not very susceptible to hydrolysis, high levels of moisture (above 10%) in the initial batches led to partial hydrolysis of the acid chloride groups upon drying. This results in high levels of **4** in the final product. The use of a two-phase system for the hydrolysis/crystallisation, e.g. methylene chloride/water[11] or toluene/water, gives rise to a finely divided precipitate, which is difficult to centrifuge, and to a very high moisture content. From these observations, it has been concluded that the use of a water-miscible cosolvent as the organic component in the crystallisation system will be more advantageous. Fructamine SA claims to have obtained good results with diglyme.[8] Since this solvent has several disadvantages, e.g., it is highly toxic, relatively expensive, and difficult to remove due to its high boiling

(13) Levin, D. *Org. Proc. Res. Dev.* **1997**, *1*,182.

(14) The N-sulfinyl intermediate has been described in a patent by Fructamine: ref 8.

point, we have resorted to the use of acetone as a more attractive alternative. The water, necessary for hydrolysis of **6**, is added as a 10% solution in acetone to a solution of **6** in acetone. This avoids immediate precipitation of product **5** and intermediate **6**, due to a local high concentration of water at the point of addition.

Apart from the N-sulfinyl intermediate **6** and the starting material **4**, two other impurities have been observed, which sometimes exceed the 1% content level in the final product. To identify and quantify their appearance, they have been isolated by silica gel column chromatography. In this way, small amounts of about 90% pure samples of both byproducts have been obtained. Due to the impurity of the material, the small quantity, the presence of only quaternary C atoms, and the presence of atropoisomers,[15] NMR analysis gives no conclusive evidence on their structure. With the additional use of infrared and mass spectral data, the dimeric amide **7** and dimeric anhydride **8** have been assigned to these impurities. The formation of both impurities is dependent on the reaction conditions, with higher levels formed at elevated temperatures. By performing the bulk of the reaction at 50−60 °C and increasing the temperature to 80 °C for a limited interval at the end of the reaction to ensure completion, the amounts of **7** and **8** have been kept under control. Depending on the crystallisation procedure, a further reduction of all impurities to levels below 1% each has been achieved.



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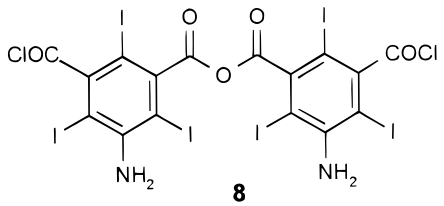

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Factorial Experimental Design

As mentioned before, the crystallisation process appears to be crucial for good-quality end-product, and we have carefully elaborated the optimal conditions for the hydrolysis/crystallisation in going from N-sulfinyl compound **6** to the end-product **5**. Good-quality **5** has to meet the following criteria: level of N-sulfinyl intermediate **6** below 1%, total purity of **5** above 97%,[16] easy to centrifuge, and low moisture content. With the knowledge of the previous experiments, a list of seven expected critical parameters in this process (X_1−X_7) has been set up, as shown in Table 1. Their number and likely interactions between them has made us decide to apply a fractional factorial design.[17]

Table 1. **Variables and maximum and minimum levels used in the factorial design**[a]

X_i	variable	(−)	0	(+)
X_1	toluene (%)	2	5	8
X_2	acetone (g)	43.5	53	62.5
X_3	temperature (°C)	25	35	45
X_4	dosing time (h)	1	2	3
X_5	final H_2O concn (%)	30	32.5	35
X_6	agitation (rpm)	280	340	400
X_7	stirring time (h)[b]	1	12.5	24

[a] All experiments were performed with the same batch of crude N-sulfinyl compound **6** (each run with 64.2 g, ∼0.1 mol of **6**). [b] Stirring time between addition of water and isolation of the product.

Table 2. **Factorial design: experimental matrix and results**

	variables							responses			
exp.	X_1	X_2	X_3	X_4	X_5	X_6	X_7	yield (%)	assay (%)	NSO (%)	*d* (g/mL)
1	−	−	−	+	+	+	−	87.2	97.9	3.6	1.4
2	+	−	−	−	−	+	+	84.0	98.2	2.4	1.4
3	−	+	−	−	+	−	+	88.9	97.9	1.7	1.7
4	+	+	−	+	−	−	−	83.0	98.3	1.8	1.7
5	−	−	+	+	−	−	+	88.0	97.8	2.4	1.2
6	+	−	+	−	+	−	−	86.6	98.1	1.7	0.9
7	−	+	+	−	−	+	−	78.9	98.0	0.7	2.0
8	+	+	+	+	+	+	+	85.2	97.5	1.0	1.9
9	+	+	+	−	−	−	+	85.8	97.7	0.3	1.6
10	−	+	+	+	+	−	−	84.9	97.9	0.7	1.7
11	+	−	+	+	−	+	−	85.7	98.1	1.0	1.3
12	−	−	+	−	+	+	+	86.3	97.9	1.7	1.9
13	+	+	−	−	+	+	−	81.9	97.6	0.3	1.4
14	−	+	−	+	−	+	+	84.9	97.2	1.1	1.3
15	+	−	−	+	+	−	+	85.3	98.3	1.6	1.3
16	−	−	−	−	−	−	−	85.4	97.8	2.5	1.2
17	0	0	0	0	0	0	0	83.0	98.6	1.3	1.4
18	0	0	0	0	0	0	0	85.8	98.4	1.5	1.8

The selection of the levels for the different factors has been carried out considering previous experiments, large-scale possibilities and limitations, and economic motives. For example, the amount of residual toluene in the final crystallisation mixture will be dependent on the efficiency of the solvent evaporation in the N-sulfinyl intermediate **6** step. A final concentration of toluene of less than 2% is difficult to reach; more than 8% can lead to heterogeneous solvent mixtures during water addition. The selected maximum and minimum levels of each factor in the factorial design are shown in Table 1.

With these variables, a scheme of 18 experiments has been setup with 16 different combinations of maximum and minimum levels of each variable, and two centre point experiments where all levels are chosen at an intermediate value (0 in Table 1). Subsequently, the experiments have

(15) (a) Henrichs, P. M.; Estep, K.; Musza, L. L.; Rodger, C. A. *J. Am. Chem. Soc.* **1995**, *117*, 2058. (b) Anelli, P. L.; Bracchetta, M.; Calabi, L. Secchi, C.; Uggeri, F.; Verona, S. *Tetrahedron* **1997**, *53*, 11919.

(16) The purity of **5** was determined by reversed-phase HPLC and is given in area %.

(17) Box, G. E. P.; Draper, N. R. *Empirical model-building and response surfaces*; John Wiley & Sons: New York, 1987.

Table 3. **Factorial design: statistical analysis and influence of variables[a,b]**

yield		N-sulfinyl	cake density	
variables	interactions	**6** variables	variables	interactions
$b_0 = 85.1$	$b_2b_5 = 0.37$	$b_0 = 1.54$	$b_0 = 1.50$	$b_1b_3 = -0.07$
$b_1 = -0.44$	$b_2b_6 = -0.60$	$b_1 = -0.27$	$b_1 = -0.06$	$b_2b_3 = 0.07$
$b_2 = -0.94$	$b_2b_7 = 1.35$	$b_2 = -0.57$	$b_2 = 0.16$	$b_2b_6 = -0.09$
$b_4 = 0.40$		$b_3 = -0.35$	$b_3 = 0.07$	$b_3b_6 = 0.13$
$b_5 = 0.66$			$b_6 = 0.08$	
$b_6 = -0.86$				
$b_7 = 0.93$				

[a] Number of experiments = 16. Degrees of freedom = 15. [b] Only significant values are given.

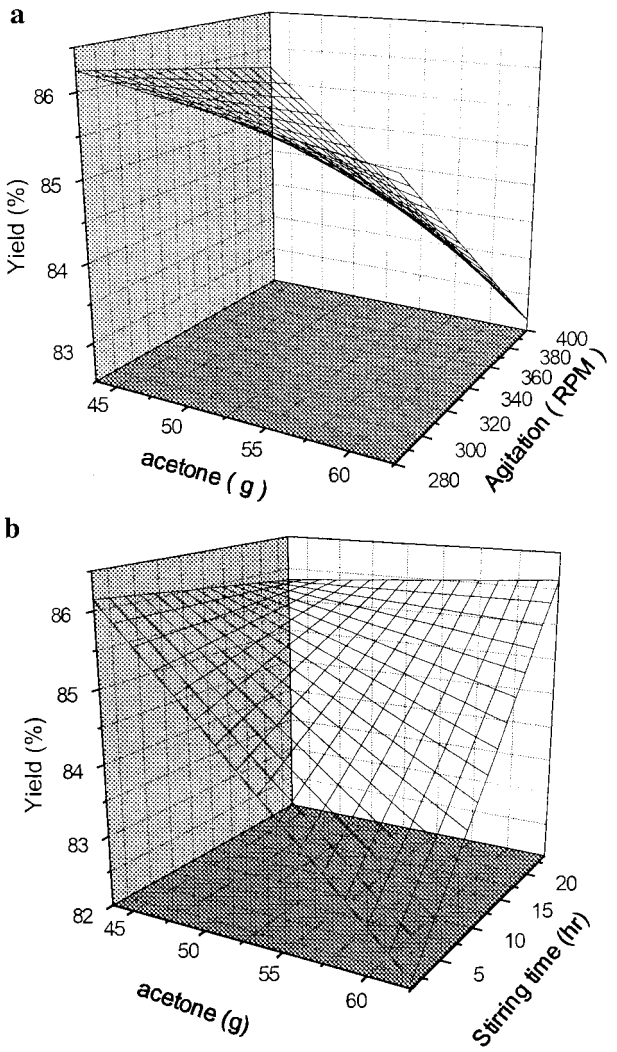

Figure 1. **(a) Influence of the amount of acetone (X_2) and the agitation (X_6) on the yield of 5. Other variables: toluene, 5%; temperature, 35 °C; dosing time, 2 h; final H_2O concn, 32.5%; final stirring time, 12.5 h. (b) Influence of the amount of acetone (X_2) and final stirring time (X_7) on the yield of 5. Other variables: toluene, 5%; temperature, 35 °C; dosing time, 2 h; final H_2O concn, 32.5%; agitation, 340 rpm.**

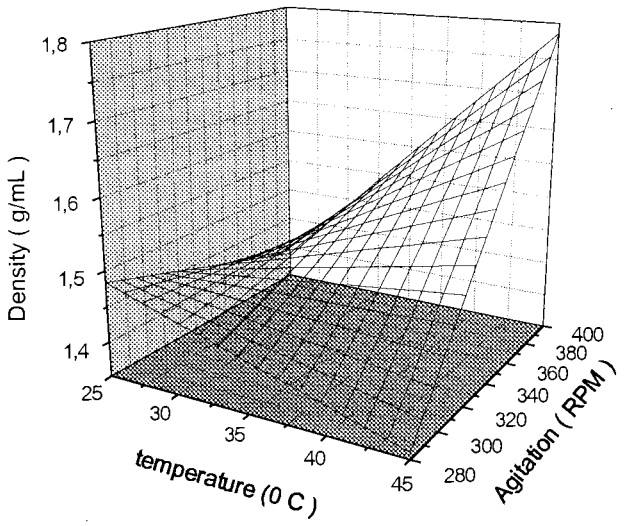

Figure 2. **Influence of the temperature (X_3) and agitation (X_6) on the cake density of 5. Other variables: toluene 5%; acetone 53 g; dosing time 2 h; final H_2O conc. 32.5%; final stirring time 12.5 h.**

Table 4. **Calculated and found results for different sets of variables**

	variables							responses			
exp.	X_1	X_2	X_3	X_4	X_5	X_6	X_7	yield (%)	assay (%)	NSO (%)	d (g/mL)
1 calcd	+	+	0	−	−	+	−	78.7	98.0	0.7	1.6
1 found								78.9	97.8	0.7	1.5
2 calcd	−	−	0	+	+	−	+	87.2	97.7	2.4	1.2
2 found								89.9	97.6	1.8	1.1
3 calcd	+	+	+	−	+	+	+	84.8	97.4	0.3	1.8
3 found								85.5	97.8	0.6	1.6

been performed at random, and for each experiment the yield and three responses to determine various quality aspects have been measured. As mentioned above, important quality parameters are the level of N-sulfinyl byproduct **6** (NSO (%)) and the overall purity of **5** (assay (%)). The density of the filter cake (d (g/mL)) has been chosen as a final response, since it shows a good correlation with both the ease of centrifugation and the moisture content of the product. Moreover, it can be easily determined and related to results obtained on large scale. In Table 2 the experimental matrix of the factorial design is shown, including the results.

The statistical analysis and the significant influences of this factorial design—using the Modde program[18]—are summarised in Table 3. The coefficients b_i have been calculated for each response using a polynomial function of the seven experimental variables as given in the following equation:

$$\text{response} = b_0 + Sb_iX_i + Sb_{ij}X_iX_j \qquad (1)$$

Only significant values are given in Table 3. Since the assay of all samples is above 97% and no variable has a major influence on this purity, these data are neglected in Table 3.

Based on the data from Table 3, various responses may be described, at 95% confidence level, as a polynomial equation with the main significant variables. This gives

(18) Modde 4.0, Umetri AB, Umeå, Sweden.

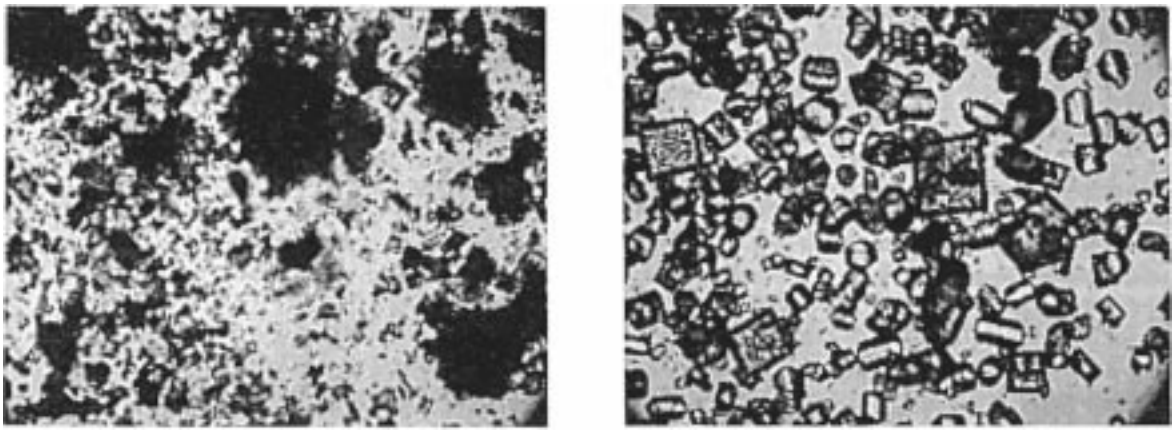

Figure 3. **Isolated 5-amino-2,4,6-triidoisophthalic acid dichloride (5) before (a) and after (b) optimisation.**

yield:

$$Y\,(\%) = 85.1 - 0.44X_1 - 0.94X_2 + 0.4X_4 + 0.66X_5 - 0.86X_6 + 0.93X_7 + 0.37X_2X_5 - 0.6X_2X_6 + 1.35X_2X_7 \quad (2)$$

N-sulfinyl intermediate **6**:

$$\mathrm{NSO}\,(\%) = 1.54 - 0.27X_1 - 0.57X_2 - 0.35X_3 \quad (3)$$

cake density:

$$d\,(\mathrm{g/mL}) = 1.50 - 0.06X_1 + 0.16X_2 + 0.07X_3 + 0.08X_6 - 0.07X_1X_3 + 0.07X_2X_3 - 0.09X_2X_6 + 0.13X_3X_6 \quad (4)$$

In general, the effects are rather small, but this is to be expected when an optimisation is carried out close to the optimal result. Still, interpolation of the data, calculated with Modde, gives a variation in the yield of the reaction between 78.7% and 87.2%. Experimental backing of the calculated model has been obtained by performing the reaction using the variable settings which predicted the lowest and highest yields, respectively (Table 4, experiments 1 and 2, respectively.). This results in yields of 78.9% and 89.9%, respectively, in excellent accordance with the theoretical yield.

The observed effects of the separate variables are largely as expected. Increased amounts of organic solvent, toluene (X_1, $b_1 = -0.44$) as well as acetone (X_2, $b_2 = -0.94$), lead to a lower yield. More water (X_5, $b_5 = 0.66$), longer addition time (X_4, $b_4 = 0.4$), and longer stirring time (X_7, $b_7 = 0.93$) all promote a better crystallisation, and thus a higher yield. Additional information is collected from the significant interactive effects between the variables. In Figure 1a, the influence of the amount of acetone and the agitation on the yield are depicted graphically. The negative effect of increased amounts of acetone gets more pronounced with increased agitation. This can be explained by an increased hydrolysis of the acid chloride **5** to the phthalic acid **4**. Indeed, a higher level of **4** is detected in the mother liquor when more acetone is used in combination with high agitation.

An even stronger interaction is observed between the amount of acetone and stirring time (Figure 1b). A clear drop in the yield is observed when an increased amount of acetone is combined with a short stirring time after addition of the total amount of water. Apparently, the rate of crystallisation is decreased in a solvent mixture with a higher percentage of acetone. Application of longer stirring times should ensure a high yield.

Unfortunately, a high yield of above 89% is accompanied by an increased level of N-sulfinyl **6**. Influential parameters on the level of **6** are toluene (X_1), acetone (X_2), and temperature (X_3). Increased values for all three parameters shift the saturation point of **5** to a higher percentage of water. This results in a more complete hydrolysis of **6** before crystallisation, and consequently a decreased level of **6** in the crystalline mass of **5**.

As mentioned before, the cake density is related to the ease of centrifugation and moisture content of the isolated product. In general, a high cake density corresponds to large crystals, a product that is easy to centrifuge, and a low moisture content. A similar picture as for the level of N-sulfinyl **6** emerges from the data obtained for the cake density. A high amount of acetone and high temperature during hydrolysis/crystallisation keeps the product **5** longer in solution and shift the precipitation of **5** more towards crystallisation. In this case, however, a high percentage of toluene gives rise to a decrease in cake density (X_1, $b_1 = -0.06$). Unfortunately, coupling of high cake density with low moisture content and ease of centrifugation cannot be made in this respect. More toluene leads to a rounder crystal form, and although this results in a decreased cake density, it appears to be favourable for the isolation of the product.

Agitation has a pronounced effect on the cake density. In Figure 2, the influence of temperature and agitation on the cake density is depicted. A combination of high temperature and high agitation increases the cake density. A high agitation is necessary to prevent the heavy crystals from settling on the bottom of the reactor. This results in growth of the existing crystals instead of the constant formation of new crystal nuclei. Although generally higher agitation rates give rise to increased attrition, the formation of smaller particles through collision does not play a dominant role. High temperatures can amplify this effect by constant redissolving of newly formed particles. Here again, precipitation of the product is shifted towards crystallisation.

Combination and incorporation of all the observations described above lead to a set of process parameters as shown in Table 4 for experiment 3. The product obtained by application of this experimental setup meets all criteria

regarding purity, yield, and moisture content and is easy to centrifuge. A picture of the crystalline product is shown in Figure 3b. Comparison with a sample prepared before initiation of the optimisation study (Figure 3a) clearly shows the effect of shifting the process from precipitation towards crystallisation.

In conclusion, the careful examination of the reaction conditions has resulted in a scaleable process with an extremely high productivity. The application of factorial design for the workup of the reaction has given us the tools to set up a procedure where the original precipitation of the product **5**, with all its isolation problems, has been shifted to crystallisation of **5**, leading to excellent quality material which is easy to centrifuge and has a very low (2−4%) moisture content.

Experimental Section

Commercially available solvents and reagents were used without further purification. 5-Amino-2,4,6-triiodoisophthalic acid was prepared according to literature procedures.[12]

Reversed-phase HPLC elutions were performed on a Lichrospher 100 RP-18 column (5 mm) with H_2O/CH_3CN mixtures. For straight-phase HPLC, a Lichrospher 100DIOL column (5 mm) was used, with eluents hexane/EtOAc/trifluoroacetic acid 70/30/0.1. ^{13}C NMR spectra were determined using a Bruker ACF 200 (50.31 MHz) spectrometer. Infrared spectra were obtained using a Perkin-Elmer Paragon 1000 FT-IR. MS data were obtained via ESI on a Finnigan Navigator LC−MS.

Representative Procedure for the Synthesis of 5-Amino-2,4,6-triiodoisophthalic Acid Chloride (5). Thionyl chloride (1.43 kg, 1.2 mol) was added to 5-amino-2,4,6-triiodoisophthalic acid (600 g, 1,07 mol). After addition of tetramethylurea (2.9 g, 25 mmol), the slurry was stirred at 50−60 °C for 6 h, during which time the solids dissolved. After the reaction mixture was heated for 30 additional minutes at 80 °C, the excess of $SOCl_2$ was distilled off under reduced pressure, thus enabling recovery of 806 g of $SOCl_2$, which could be used in subsequent batches. To remove the remaining $SOCl_2$ from the residue, the solid was dissolved in 500 mL of toluene (at 50−60 °C) and subsequently concentrated under reduced pressure to give the crude 5-sulfinylamino-2,4,6-triiodoisophthalic acid chloride (**6**). The residue was dissolved in acetone (584 g, 738 mL) and warmed to 45 °C. At this temperature, a 90/10 w/w acetone/water mixture (449 g, 550 mL) was added dropwise to the solution over a 1-h period. After the solution was stirred for an additional hour and cooled to 25 °C, water (487 mL) was added dropwise over a 2-h period. Stirring was continued for 24 h, and the crystals were recovered by filtration (small scale) or centrifugation (large scale). The cake was washed with 400 mL of acetone/water 50/50 (w/w), followed by 400 mL of water, to give a wet product with a moisture content of 2−4%. Drying was performed at 40 °C under vacuum to give 547 g of **5** (85.5%). Analytical and spectroscopic data were identical to those described in ref 12.

Isolation and Identification of Major Byproducts. The mother liquor, obtained from the previous step and enriched in byproducts, was concentrated under reduced pressure, and a few grams of the residue was dissolved in a minimal amount of toluene/EtOAc 6/1. Silica gel chromatography of this solution (eluent hexane/EtOAc, 70/30 to 50/50) provided, in order of elution, samples of **7** and **8**.

***N*-5′-Amino-2′,4′,6′-triiodo-3′-chlorocarbonylbenzoyl-2,4,6-triiodo-3,5-di(chlorocarbonyl)aniline Amide (7).** ^{13}C NMR (acetone-d_6) (clearly distinguishable signals): δ 59.23, 60.60, 67.03, 72.90, 76.44, 79.40, 146.15, 149.75, 150.07, 150.44, 161.72, 170.04. IR (cm^{-1}): ν 1761 (br s), 1673 (s), 1596 (s), 1528 (m), 1487 (s), 1393 (m), 1354 (s), 1046 (m), 999 (s), 962 (m). MS ($M - H^+$): *m*/*z* 1152, with a Cl isotope pattern of 3:3:1.

5-Amino-2,4,6-triiodo-3-chlorocarbonylbenzoic Anhydride (8). ^{13}C NMR (DMSO-d_6) (clearly distinguishable signals): δ 61.03, 73.13, 95.89, 142.52, 149.78, 169.60, 170.40. IR (cm^{-1}): ν 1806 (s), 1765 (br s), 1594 (s), 1515 (m), 1398 (s), 1312 (m), 1268 (m), 1074 (s), 1005 (s), 917 (s). MS ($M - H^+$): *m*/*z* 1134, with a Cl isotope pattern of 9:6:1.

Received for review June 25, 1998.

OP980055+