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N-Acylation Reactions Performed in Aqueous Reaction Medium: Screening and Optimising of a Synthetic Step of a Process for Iodixanol

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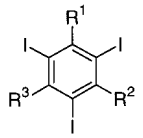
Abstract:

This contribution presents results from a development and optimisation project concerning a synthetic process for iodixanol. Iodixanol is the "active ingredient" in Visipaque (Nycomed Amersham now Amersham Health) a medical X-ray imaging contrast agent. The process step that was developed and optimised comprised a reaction between a tetraacid chloride and 3-aminopropane-1,2-diol for obtaining the corresponding tetraamide. This reaction was originally performed using DMA as reaction medium, a reaction that gave a medium-to-high yield of the tetraamide. Solvent screening was performed followed by process optimisation using response surface methodology. Surprisingly, a solvent mixture composed by 1:2 v/v THF:water was determined to be a superb reaction medium. Tuning the experimental condition according to the developed multivariate empirical model gave an excellent yield of the target molecule, nearly 94% with only small quantities of the main side product, monoacid triamide, which indicates a rather low hydrolytic degradation of the substrate. The current synthetic process step to iodixanol showed also a general validity when a small variety of amino alcohols and acid chlorides were reacted to successfully obtain the desired amides in high yields, concomitant with low outcomes of the most likely side products, that is the hydrolysis products of the acid chlorides.

Introduction

Generally, X-ray contrast agents for medical imaging diagnostics[1] are compounds that contain at least one triiodobenzene moiety **1**. This moiety can be considered as the main "*pharmacophore*" in such compounds, since it is this part that gives the desired effect, the X-ray absorption. However, iodine has lipophilic properties, which imply that it is necessary to introduce some other moieties that can counteract that property. Hence, the R^1, R^2, and R^3 groups of the molecule must then have a high degree of hydrophilic character. Examples of such groups are carboxyl, carboxamide, hydroxyl, alkoxyl, and glycosyl, and so forth. Moreover, the R^1, R^2, and R^3 groups of the substances of type **1** are also designed to "regulate" the pharmacokinetic profile of the entire compound.

Two desirable features are good water solubility and low viscosity. However, the composition of the side chains will also influence the chemotoxicity of the entire compound. The triiodo aromatic compounds are classified as first- or second-generation X-ray contrast agents, depending on whether the compound contains ionic or nonionic groups, respectively. Third generation contrast agents are nonionic agents composed of two nonionic triiodo aromatics, such as compound **1**, which are connected by a C_3 or C_4 bridge. Iodixanol[2,3] **2** (Scheme 1) is an example of a compound with a C_3 bridge. Clinical tests of formulations of iodixanol **2** have shown many improved advantages over earlier generations of X-ray contrast agents, moreover iodixanol **2** is isotonic and isoosmotic with blood.[4]



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Many of the X-ray contrast agents commercially available today have in common that two of the side chains (R^1 and R^2) are carboxamides. The carboxamide group is found to be very suitable in X-ray contrast agents due to in situ stability as well as low contribution to the final chemotoxicity of the compound. However, the N-acylation or amidation reaction step in the synthesis of these compounds involves reacting water-soluble amines (the side chains) with water-insoluble substrates (the triiodinated moiety). This situation makes it difficult to select a suitable solvent for the reaction, especially if aprotic solvents such as dimethylformamide (DMF) and dimethylacetamide (DMA) have to be omitted due to (1) their high boiling points and the consequent difficulties of removal from the bulk drug substance, (2) their toxicity and thus the environmental aspect, (3) the costs, and (4) the fact that the solvents DMA and DMF are not inert under the applied reaction conditions, where for example DMF may participate in a Vilsmeyer−Haack,[5−7] reaction.

The present contribution will describe a process for introduction of the side chains of the X-ray contrast agent iodixanol **2**. This synthetic process comprises concomitant formation of four carboxamide side chains giving the

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(2) Hansen, P.-E.; Holtermann, H.; Wille, K. (Nyegaard & Co AS, Oslo, Norway). EP 0 108 638, 1984.

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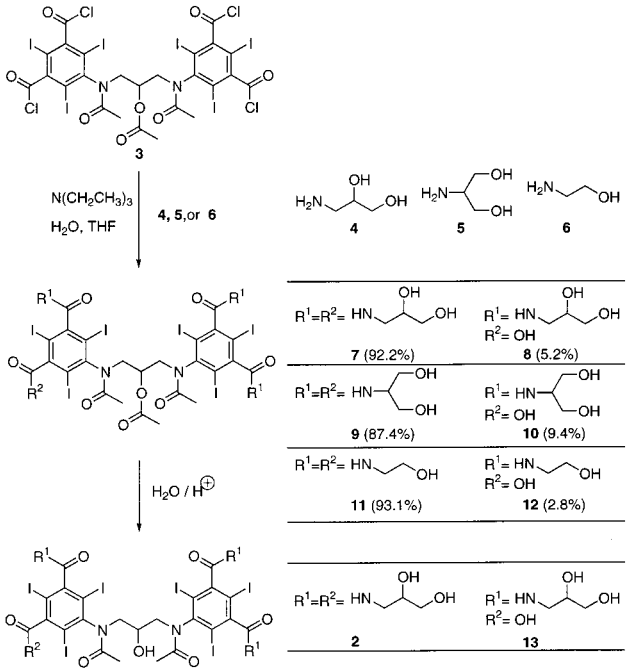
Scheme 1



intermediate **7**. A competing process is the hydrolysis of the acid chloride under formation of the side product **8**, Scheme 1.

Methods and Results

The synthetic transformation **3** + **4** → **7**, Scheme 1, is carried out by reacting racemic 3-aminopropane-1,2-diol **4** with the tetraacid chloride **3** using triethylamine as HCl scavenger. The target molecule of this reaction 3,3′,5,5′-tetrakis(2,3-dihydroxypropylcarbamoyl)-2,2′,4,4′,6,6′-hexaiodo-*N*,*N*′-(2-hydroxy-*O*-acetyl propane-1,3-diyl)diacetanilide **7** was of interest as a final intermediate in a process leading to 3,3′,5,5′-tetrakis (2,3 − dihydroxypropylcarbamoyl)-2,2′,4,4′,6,6′-hexaiodo- *N*,*N*′-(2-hydroxypropane-1,3-diyl)-diacetanilide **2** (iodixanol) that is used as a racemic mixture in Visipaque (Nycomed Amersham).

One of the major challenges of this synthetic transformation was to find a solvent system suitable for industrial-scale production, as well as to determine the conditions under which the reaction should be performed to obtain a selective high-yielding procedure. During the screening phase of the organic process development, it was observed that the substrate **3** was soluble in tetrahydrofuran, but not in water, while reagent **4** and the reaction intermediates were soluble in water. Even though water is not considered as a particularly suitable reaction medium for acid chlorides, some very introductory experiments were performed using water as solvent/cosolvent for the "amidation" reaction, step 1 of Scheme 1. Surprisingly, high yields of the target molecule were achieved with only a small quantity of the tetraacid chloride **3** being hydrolyzed to the corresponding mono, di-, tri-, or tetracarboxylic acid, under the aqueous reaction conditions. The major by-product was the monocarboxylic acid **8**, even if only in small quantities. Besides these promising results, the solvent mixture of water and tetrahydrofuran fulfilled also the requirements with respect to the cost, the boiling point of the solvent(s), the environmental effects, and so forth. On the basis of these findings we decided to carry through a process optimisation of the N-acylation reaction using the solvent/cosolvent mixture of water and tetrahydrofuran. A thorough examination of the procedure showed that eight experimental/process variables were likely to influence the reaction. Figure 1 shows the variables represented in an *Ishikawa cause-effect* diagram.

Since the outcome of the introductory synthetic procedure gave quite a high yield (∼75%) when measured using HPLC, it was decided to use a response surface design[8] for the further development of the synthetic procedure. Four of the eight experimental variables (see Figure 1) were expected to have the major influence on the synthetic reaction, and were thus further explored. The experimental variables the amount of water (x_1), the amount of tetrahydrofuran (x_2), the amount of the reagent 3-aminopropane-1,2-diol **4** (x_3), and the reaction temperature (x_4) were used in a circumscribed central composite design (CCC) with seven replicates of the centre point experiment, giving for $k = 4$ variables a design composed of $2^k + 2k + 7 = 31$ experiments. The other experimental variables, such as stirring rate, reaction time, and quantity of HCl scavenger may well all be influencing variables. By using sufficient long reaction time, sufficient stirring rate, and a quantity of HCl scavenger that was at least as much as the HCl that was developed during the reaction, these variables did not perturb the reaction in a negatively manner.

The selected experimental levels for the variables (x_1, ..., x_4) are given in Table 1. The CCC design allowed estimation of the regression coefficients for the variables (x_1, ..., x_4), for the two-factor interactions ($x_1 \times x_2$, $x_1 \times x_3$, ..., $x_3 \times x_4$) as well as for the quadratic terms (x_1^2, ..., x_4^2).

The results obtained in the laboratory experiments, HPLC measurements y (Table 1), were used as the response variable and were thus regressed onto the experimental variables including their interaction- and quadratic terms (constitutes the model matrix), by using the PLSR method,[9] $y = f(x_1, ..., x_4, x_1^2, ..., x_4^2, x_1 \times x_2, x_1 \times x_3, ..., x_3 \times x_4)$ The estimated regression coefficients (the β's in Table 2) were plotted in a CND (cumulative normal distribution) plot, Figure 2, corresponding statistical analysis and estimated values for the regression parameters are listed in Table 2. The CND plot in Figure 2 and data in Table 2, both lead to the conclusion that the regression coefficients β_3, β_4, β_{33}, and β_{44} were statistically significant and thus contribute to explanation of the variation in the response y. The estimates β_1 and β_{22} are, however, "borderline cases" and were included in the model. Moreover, β_{23} and β_{24} are not significant on the basis of strictly statistical assessments, but are included when using the more rough method of variable selection using CND plot (Figure 2). The model that was estimated for the optimisation of the reaction, **3** + **4** → **7**, Scheme 1, is given in eq 1. The model was estimated by using $a = 5$ PLS components that explaining 99.84% of the variation in y when using cross-

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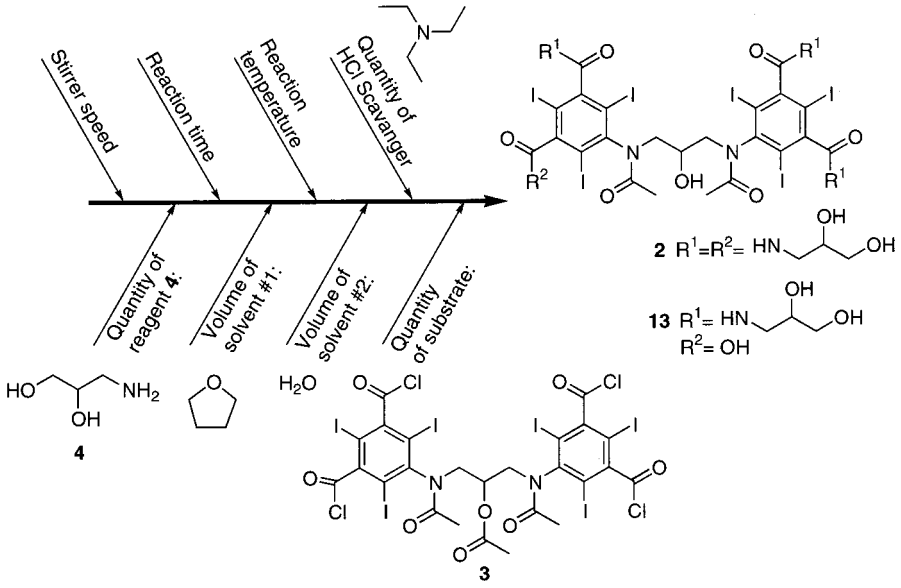


Figure 1. **Ishikawa cause−effect diagram.**

Table 1. **Central composite design with response *y*, the yield of product 6 in the N-acylation reaction**

exp. no.	experimental variables[a] x_1	x_2	x_3	x_4	response[b] y	exp. no.	experimental variables[a] x_1	x_2	x_3	x_4	response[b] y
1	−1	−1	−1	−1	78.9	17	−2	0	0	0	88.2
2	+1	−1	−1	−1	83.7	18	+2	0	0	0	80.0
3	−1	+1	−1	−1	71.7	19	0	−2	0	0	72.0
4	+1	+1	−1	−1	67.4	20	0	+2	0	0	81.6
5	−1	−1	+1	−1	92.3	21	0	0	−2	0	59.8
6	+1	−1	+1	−1	90.6	22	0	0	+2	0	87.6
7	−1	+1	+1	−1	89.2	23	0	0	0	−2	91.3
8	+1	+1	+1	−1	87.7	24	0	0	0	+2	86.7
9	−1	−1	−1	+1	67.4	25	0	0	0	0	82.0
10	+1	−1	−1	+1	71.2	26	0	0	0	0	80.3
11	−1	+1	−1	+1	71.9	27	0	0	0	0	80.0
12	+1	+1	−1	+1	64.8	28	0	0	0	0	79.0
13	−1	−1	+1	+1	89.6	29	0	0	0	0	80.9
14	+1	−1	+1	+1	77.7	30	0	0	0	0	80.9
15	−1	+1	+1	+1	82.1	31	0	0	0	0	80.1
16	+1	+1	+1	+1	80.8						

[a] The experiments were performed using 50 g *O*-acetyl-iodixanol **3** in each experiment. *Experimental variables:* x_k (definition) [levels: −2, −1, 0, +1, +2]; x_1 (amount of water) [12.5, 25.0, 37.5, 50.0, 62.5 mL]; x_2 (amount of tetrahydrofuran) [0, 50, 100, 150, 200 mL]; x_3 (amount of 3-aminopropane-1,2-diol) [11.443, 13.931, 16.499, 18.906, 21.394 g]; x_4 (reaction temperature) [10, 20, 30, 40, 50, °C]. Mean value for the center experiment ($y = \sum_{i=25}^{31} y_i/7$) is 80.457. [b] Yield% measured by HPLC analysis.

validation[10] for PLS via NIPALS with random split and 20 iterations. The product statistics for the model were for this model $R^2 = 0.8497$ and $Q^2 = 0.5176$, that demonstrates a fairly good model for prediction purpose.

$$y = \beta_0 + (\beta_1 x_1) + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4 + (\beta_{22} x_2^2) + \beta_{33} x_3^2 + \beta_{44} x_4^2 + (\beta_{23} x_2 x_3 + \beta_{24} x_2 x_4) = 81.0957 - 1.4833\, x_1 - 0.6917 x_2 + 7.0250 x_3 - 2.7167 x_4 - 1.2662 x_2^2 - 2.0412 x_3^2 + 1.7838 x_4^2 + 0.9375 x_2\, x_3 + 1.4500 x_2 x_4 \quad (1)$$

The model of eq 1 was used for the preparation of the multidimensional contour plot of Figure 3. The isocontour projection of the response surfaces shown in Figure 3 actually describes variation in one response, the yield of **7**, in five dimensions. The five dimensional response surface is given by the contour lines and the four experimental variables (x_1, ..., x_4). This plot is used in the following way: consider the outer frame which shows the variation of the two experimental variables x_1 and x_2 at three discrete levels −1, 0, and +1 (x_1 [25.0, 37.5, 50.0 mL] and x_2[50, 100, 150 mL]). Inside this frame, the nine subplots show the contour projections of the response surface when the other two experimental variables x_3 and x_4 are varied continuously between the limits, here −2 and +2 (x_3 [11.4 → 21.4 g] and x_4[10 → 50 °C]).

The contour plots represented in Figure 3 reveal that to obtain a high yield of target molecule **7**, it is advantageous to apply a high quantity of 3-aminopropane-1,2-diol **4** (variable x_3). However, by also tuning the other experimental variables, the combined goal of high yield at less cost may be achieved. Thus by using a lowered reaction temperature (variable x_4) and a concentrated reaction mixture (lowered

Table 2. **Numerical estimates for the model for the yield in the N-acylation reaction**

yield	coefficient	standard error	*P*	confidence interval
β_0	80.476	1.552	$2.966\ 10^{-19}$	±3.291
β_1	−1.471	0.838	0.099	±1.777
β_2	−0.694	0.838	0.420	±1.777
β_3	7.017	0.838	$3.074\ 10^{-7}$	±1.777
β_4	−2.714	0.838	0.005	±1.777
β_{11}	0.620	0.768	0.432	±1.628
β_{22}	−1.217	0.768	0.133	±1.628
β_{33}	−1.980	0.768	0.020	±1.628
β_{44}	1.848	0.768	0.029	±1.628
β_{12}	−0.565	1.027	0.590	±2.177
β_{13}	−0.847	1.027	0.421	±2.177
β_{14}	−0.870	1.027	0.409	±2.177
β_{23}	0.944	1.027	0.372	±2.177
β_{24}	1.451	1.027	0.177	±2.177
β_{34}	−0.194	1.027	0.853	±2.177

[a] Number of objects = 31, $R^2 = 0.8713$, $Q^2 = 0.4179$, $R^2_{Adj} = 0.7587$, RSD = 4.0723, confidence level = 0.95.

(10) Wold, S. *Technometrics* **1978**, *20*, 397.

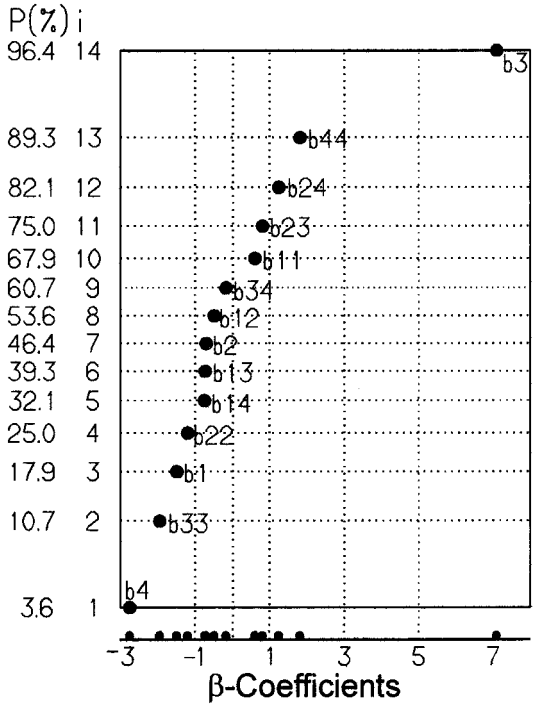


Figure 2. **CND plot.**

volumes of the two solvents water and tetrahydrofuran, variables x_1 and x_2) the quantity of the reagent **4** may be lowered to obtain a high yield of target molecule **7**. Thus, the combined goals for a good process are achieved, high yield, increased reactor volume efficiency, and improved environmental performance by solvent replacement.

Optimized and Scaled Up Experiments

Optimized Experiments. The multivariable model obtained from the statistically designed experimental plan was finally used for predicting the optimal conditions that should preferably give a quantitative yield. The procedure predicted by the model: the tetraacid chloride **3** (50 g, 0.0364 mol) was dissolved in a mixture of tetrahydrofuran (50 mL), water (25 mL), and triethylamine (16.5 g, 0.163 mol, ∼4.5 equiv) at a temperature of 10 °C. The reagent 3-aminopropane-1,2-diol **4** (21.4 g, 0.2349 mol, ∼6.5 equiv) was then added. The reaction rate was observed to converge over a rather long period, and was determined to be "optimal" after 24 h. If the temperature was decreased further below 10 °C, the reaction was almost blocked-up. The obtained yield of compound **7** of this experiment was 94%. The remaining 6% was determined to be the main by-product monoacid triamide **8**, but traces of other by-products were also observed. These results were somewhat surprising, since acid chlorides in the presence of water are usually expected to undergo a Schotten−Baumann[11]-type reaction, yielding the corresponding carboxylic acid of the acid chloride.

Scaling Up for Pilot Plant. On the basis of the successful result achieved during the laboratory development, the synthetic method was scaled up and fitted to pilot runs. The test run was performed in a 0.5 m^3 stirred tank reactor. The reactor was charged with 40 L of water, 25.7 kg (254.7 mol) of triethylamine, 33.7 kg (370.8 mol) of the reagent **4**, and 80 L of tetrahydrofuran. The reaction mixture was cooled to a temperature of 0 °C. The tetraacid chloride **3,** 79.6 kg (57.94 mol), was added to the solution over a period of 2.5 h. The temperature was always maintained below 10 °C during the addition. The reaction mixture was continuously stirred for another 15 h at a temperature between 11 and 16 °C. At completion of the reaction, the liquid phases, the organic and the water phases, were separated. The water phase was diluted to a total volume of 400 L and the pH adjusted to 6.9. Sodium chloride was added to salt out the organics. The isolated yield was >80% with a strength of 99%.

Evaluation of the Generality of the Developed Method. To evaluate the generality of the developed synthetic method, a small variety of substrates and reagents were selected. Schemes 1−3 summarise the experimental results. For each of the acid chlorides, three different amino alcohols were tested, namely 3-aminopropane-1,2-diol **4**, 2-aminopropane-1,3-diol (serinol) **5**, and 2-amino ethanol **6**. The acid chlorides that were selected were the tetraacid chloride **3**, benzoyl chloride **14**, and 3-phenylpropionyl chloride **15**. The obtained results for the experiments that were performed with the tetraacid chloride **3** and the three amino alcohols (**4**−**6**) are given in Scheme 1. Only in the case where the serinol **5** were used, a somewhat elevated quantity of the corresponding triamide monoacid is observed (9.4%). The results for the reactions between the amino alcohols (**4**−**6**) and benzoyl chloride **14**, and the amino alcohols (**4**−**6**) and 3-phenylpropionyl chloride **15**, are given in the Schemes 2 and 3, respectively. In all of the experiments for the simple acid chlorides **14** and **15**, only traces of the two corresponding carboxylic acids, benzoic acid and 3-phenylpropionic acid, respectively.

Conclusions

Even though most textbooks of organic chemistry[12] report that acid chlorides are rather labile in the presence of water, we have developed a simple selective and high-yielding synthetic procedure for N-acylation by reacting acid chlorides with amines using a reaction medium composed of water and tetrahydrofuran. Due to the high rate of the N-acylation reaction and the relatively lower rate of the hydrolysis reaction of the acid chloride in water, only minor traces of the hydrolysis product are detected.

The method was originally developed for synthesis of 3,3′,5,5′-tetrakis(2,3-dihydroxypropyl-carbamoyl)-2,2′,4,4′,6,6′-hexaiodo-*N*,*N*′-(2-hydroxy-*O*-acetyl propane-1,3-diyl) diacetanilide **7**, an intermediate for iodixanol, reacting acetic acid 2-[acetyl[3,5-bis-chlorocarbonyl- 2,4,6 − triiodo − phenyl)amino]-1-{[acetyl[3,5-bis-chlorocarbonyl-2,4,6-triiodophenyl)methyl]}ethyl ester **3** with 3-aminopropane-1,2-diol **4**. The derived multivariate empirical model, based on

(11) (a) Schotten, C. *Berichte* **1884** *17*, 2544. (b) Baumann, E. *Berichte* **1886**, *19*, 3218. (c) Smith, M. B.; March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 5th ed.; Wiley: New York, 2001; p 482.

(12) Smith, M. B.; March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 5th ed.; Wiley: New York, 2001; p 468.

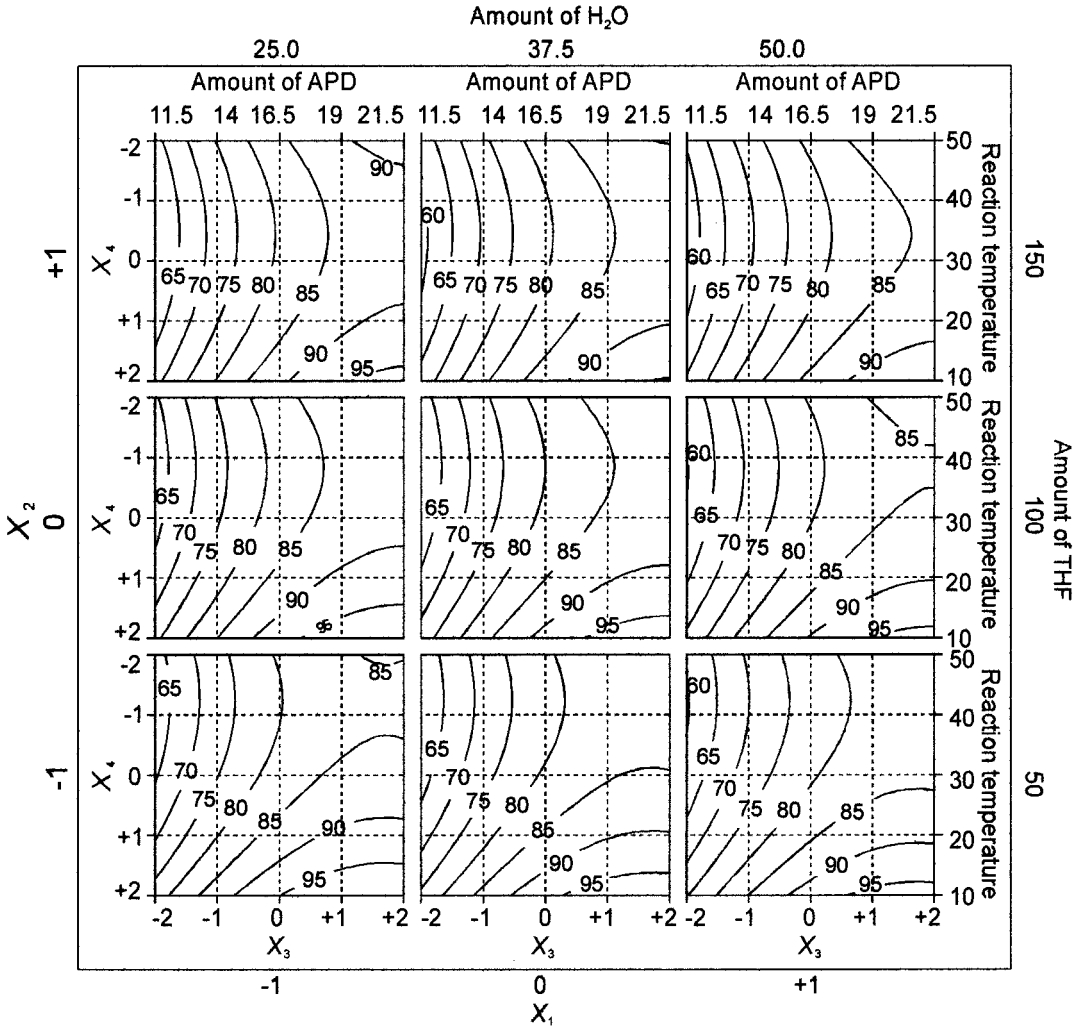
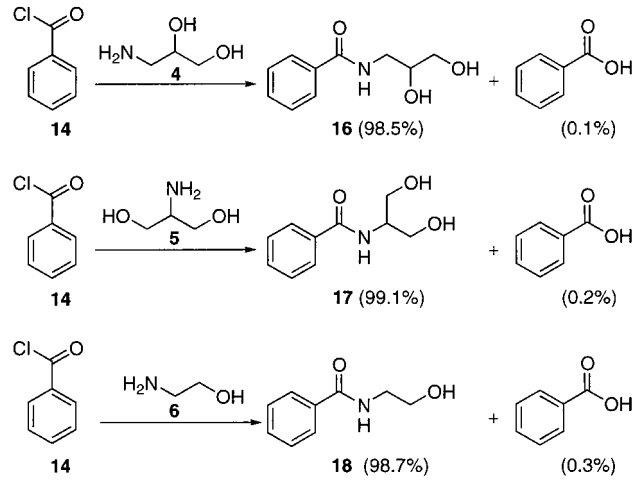


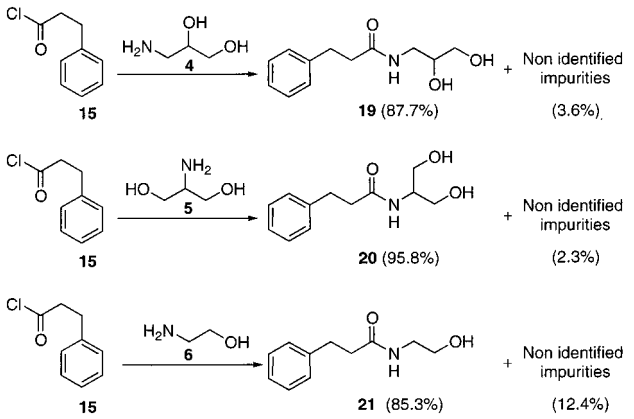
Figure 3. **Isocontour projection of the response surfaces.**

Scheme 2. **Reactions between the amino alcohols (4−6) and benzoyl chloride 14**



the statistically designed experimental plan for optimisation of the N-acylation reaction, revealed that high reaction temperature favours the formation of the triamide monoacid. When a higher quantity of 3-aminopropane-1,2-diol **4** is used, the fourth step, N-acylation, is accelerated, and the formation of the triamide monoacid **7** is thus lowered.

Scheme 3. **Reactions between the amino alcohols (4−6) and 3-phenylpropionyl chloride 15**



The model shows also that the composition of the reaction mixture is important, and predicts a good composition to be v:v = 1:2 (water:tetrahydrofuran).

A variety of amino alcohols and acid chlorides (see Schemes 1−3) were reacted under the optimised conditions determined for the synthetic process to iodixanol **2**. These experiments revealed the method as a general approach for N-acylation reactions, since very high yields were obtained

for all of the combinations tried. Moreover, except for the X-ray-absorbing derivatives, only small quantities of the hydrolysis product of the acid chlorides were found. In the experiments for the hexaiodinated substrates, the hydrolysed acid chlorides were determined to be in the range 2.8−9.4%. Even though the superb yields were achieved when using different substrates and reagents of Schemes 1−3, the reaction conditions may not be the optimum for other reagents and substrates. Such cases will require further optimization.

Experimental Section

Synthetic Procedure for Designed Experiments. In a 500 mL jacketed reaction vessel connected to an external temperature-control unit and equipped with a condenser and mechanical stirrer, *O*-acetyl-iodixanol (50 g, 0.036 mol) **3** was added to a mixture of triethylamine (16.2 g, 0.160 mol), aminopropandiol ([11.44 to 21.39] g, [0.126 to 0.234] mol), water ([12.5 to 62.5] mL), and tetrahydrofuran ([0 to 200] ml) at [10 to 50] °C. The reaction mixture was stirred at a temperature of [10 to 50] °C for a period of 18 h. At the end of the reaction two separate layers, one organic phase and one water phase were formed, where the water phase contained amidated product(s). The two phases were separated, and the water phase was diluted to a total volume of 250 mL with purified water and neutralized to pH 6.5−7.0 with concentrated HCl. One millilitre of the neutralized water phase was transferred to a 100 mL measurement flask and diluted to a total volume of 100 mL with purified water. This solution was injected onto HPLC for quantification using the method previously described.[3]

Control Experiments: Synthetic Procedure to *N*-(2-Hydroxyethyl) Benzoylamide 18 (Similar Procedure for Compounds 16, 17, 19, 20, and 21). To a 100 mL jacketed reaction vessel connected to an external temperature-control unit equipped with a condenser and mechanical stirring, water (12.5 mL), tetrahydrofuran (25 mL), triethylamine (2.00 g, 0.019 mol), and 2-hydroxyethylamine (1.75 g, 0.027 mol) were mixed and cooled to 13 °C. To the cooled mixture benzoyl chloride (2.43 g, 0.017 mol) was added, keeping the internal temperature below 20 °C during addition. The reaction mixture was stirred at 13 °C for 20 h.

HPLC analysis of the reaction mixture after 20 h. showed a conversion of starting material of 99.2% (area % HPLC at 254 nm). The chemical yields according to area % HPLC at 254 nm were 98.7% for *N*-(2-hydroxyethyl)benzoylamide **18**, 0.3% for benzoic acid and 0.15% of other reaction products.

Control Experiments: Synthetic Procedure to Compounds 7, 9, and 11. For the experiments with tetraacid chloride **3**, the procedure was similar to that given above, except that the quantities of the triethylamine were (4 × 0.019 mol = 0.076 mol), and for the amino alcohols (**4**−**6**) the quantities (4 × 0.017 mol = 0.068 mol) were used.

Spectroscopic Data. The NMR spectra were recorded on a Bruker 400 MHz NMR Spectrometer. The shift data (δ) are reported in ppm.

7: $C_{37}H_{46}I_6N_6O_{16}$, MW 1592.24. Isolated substance was compared against reference on HPLC. The reference substance is fully described in ref 3.

9: $C_{37}H_{46}I_6N_6O_{16}$, MW 1592.24.

^{1}H NMR (DMSO-d_6) 3.34 (CO−NH, broad); 2.12 (CH−O, broad); 3.86−3.57 (C*H*$_2$−OH; CH−O−(C═O)CH$_3$; C*H*−NH−CO; broad); 3.13−3.06 (m, C*H*$_2$−N); 1.79 (CH3, OH; broad).

^{13}C NMR (DMSO-d_6) 170.26; 169.90; 168.99 (C═O); 151.03 ($C_{q,\ arom}$−N); 147.15 ($C_{q,\ arom}$−C═O); 100.82; 100.55; 99.92 (C−I); 72.06 (CH$_3$−(C═O)−O−*C*−H); 59.19; 58.60 (CH2−O); 54.45; 52.95 (CH$_3$−(C═O)−N−*C*H); 45.78 (CH$_3$−(C═O)−N−*C*H); 22.74(CH$_3$); 8.54(CH$_3$).

MS-ESP+ *m*/*z*: molecule ion + H$^+$ = 1593 (85%), molecule ion + Na$^+$ = 1614.9 (100%).

11: $C_{33}H_{38}I_6N_6O_{12}$, MW 1472.13.

^{1}H NMR (DMSO-d_6) 8.66 (N−H, broad); 5.07 (broad, CH−O−(C═O)-CH$_3$) 3.79−3.58 (broad, CH$_2$−O, CH$_2$−N−(C═O)-CH$_3$); 3.25 (broad, CH$_2$−N); 1.86−1.77 (broad, CH$_3$ and OH).

^{13}C NMR (DMSO-d_6) 169.85−169.17 (C═O); 151.13 ($C_{q,\ arom}$−N); 147−147.02 ($C_{q,\ arom}$−(C═O)) 101.086−98.86 (C_q−I); 71.95 (H−*C*−O−(C═O)-CH$_3$); 59.14 (*C*H$_2$−O); 41.65 (*C*H$_2$−N); 39.75 (*C*H$_2$−N); 21.69 (*C*H$_3$).

MS-ESP+ *m*/*z*: molecule ion + H$^+$ = 1472.8, molecule ion + Na$^+$ = 1494.9

16: $C_{10}H_{13}NO_3$, MW 192.22.

^{1}H NMR (DMSO-d_6) 166.58 (C═O); 134.49 ($C_{q,\ arom}$); 130.95; 128.11; 127.11 (CH, arom); 70.37 (CH−OH); 67.98 (CH$_2$−OH); 63.90 (CH$_2$−NH).

^{13}C NMR (DMSO-d_6) 8.34 (1H, NH, broad); 7.87−7.85 (2H, m, arom); 7.51−7.42 (3H, m, arom) 3.70−3.64 (1H, m, CH−OH), 3.39−3.32 (2H, m, CH$_2$−OH) 3.25−3.20 (2H, m, CH$_2$−NH).

MS-ESP+ *m*/*z*: molecule ion + H$^+$ = 1472.8, molecule ion + Na$^+$ = 1494.9.

17: $C_{10}H_{13}NO_3$, MW 195.22.

^{1}H NMR (DMSO-d_6) 7.85 (1H, d, N−H); 7.53 (5H, m, arom); 4.58 (2H, t, OH); 3.99−3.94 (1H. m, H−C−N); 3.53 (4H, 2CH$_2$, t, CH$_2$OH).

^{13}C NMR (DMSO-d_6) 166.23 (C═O); 134.74 ($C_{q,\ arom}$); 130.88; 128.02; 127.19 (CH, arom); 60.38 (CH$_2$−OH); 53.77 (H−C−N).

MS-ESP+ *m*/*z*: molecule ion + H$^+$ = 196.0 (25%), molecule ion + Na$^+$ = 218.0 (100%), molecule ion + H$^+$ − H$_2$O = 178 (45%).

18: $C_9H_{11}NO_2$, MW 165.19.

^{1}H NMR (CDCl$_3$) 8.37 (1h, n−h, broad); 7.88−7.86 (2H, arom, m); 7.53−7.43 (3H, m, arom); 4.69 (1H, t, O−H); 3.57−3.52 (2H, q, CH$_2$−OH, J = 6.07 Hz));3.38−3.30 (2H, m, CH$_2$−NH).

^{13}C NMR (CDCl$_3$) 166.36 (═O); 134.59 ($C_{q,\ arom}$); 130.92; 128.10; 127.11 (CH, arom); 59.81 (CH$_2$−OH); 42.19 (CH$_2$−OH).

MS-ESP+ *m*/*z*: molecule ion + H$^+$ = 166.1 (100%), molecule ion + Na$^+$ = 188.1 (15%).

19: $C_{12}H_{17}NO_3$, MW 233.27.

^{1}H NMR (CDCl$_3$) 7.25−7.10 (5H, m, arom); 6.96 (1H, t, N−H, J = 5.93 Hz); 4.73 (2H, broad, OH); 3.69−3.64 (1H, m, CH−OH); 3.48−3.37 (2H, m, CH$_2$−OH); 3.33−3.18 (2H, m, CH$_2$−NH); 2.90−2.85 (2H, t, CH2−C═O, J = 6.04

Hz); 2.48−2.44 (2H, t, CH_2−Ph, J = 6.04 Hz).

^{13}C NMR ($CDCl_3$) 174.20 (C_q, C═O); 140.45 ($C_{q,\ arom}$); 128.46;128.40 128.17; 126.24; 126.14 (CH, arom); 70.83 (CH−OH); 63.60; 42.05; 37.86; 31.56 (CH_2).

MS-ESP+ *m*/*z*: molecule ion + H^+ = 224.1 (10%), molecule ion + Na^+ = 246.0 (100%).

20: $C_{12}H_{17}NO_3$, MW 223.27.

^{13}C NMR ($CDCl_3$) 172.98 (C_q, C═O); 140.86 ($C_{q,\ arom}$); 128.56; 128.48; 126.31 (CH, arom); 63.46; 38.50; 31.87 (CH_2); 52.66 (CH).

^{1}H NMR ($CDCl_3$) 7.31−7.20 (5H, arom); 2.98 (2H, CH_2−C═O, t); 2.54 (2H, CH_2−Ph, t); 3.93−3.86 (1H, CH, m); 3.78−3.64 (4H, $2CH_2$−OH).

MS-ESP+ *m*/*z*: molecule ion + H^+ = 224.1 (100%), molecule ion + Na^+ = 246.0 (70%), molecule ion + H^+ − H_2O = 206.1 (20%).

21: $C_{11}H_{15}NO_2$, MW 193.25.

^{1}H NMR ($CDCl_3$) 7.27−7.15 (5H, m, CH, arom); 6.44 (1H, broad, NH); 3.59−3.57 (2H, t, CH_2−NH); 3.32−3.29 (2H, q, CH_2−OH); 2.94−2.90 (2H, t, CH_2−C═O); 2.49−2.45 (2H, t, CH_2−Ph).

^{13}C NMR ($CDCl_3$) 173.42 (C_q, C═O); 140.60 ($C_{q,\ arom}$); 128.46; 128.21; 126.22 (CH, arom); 61.70; 42.27; 38.17; 31.65 (CH_2).

MS-ESP+ *m*/*z*: molecule ion + H^+ = 194.1 (100%), molecule ion + Na^+ = 216.0 (60%).

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