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Fine Chemicals from Lignosulfonates. 2. Synthesis of Veratric Acid from Acetovanillon

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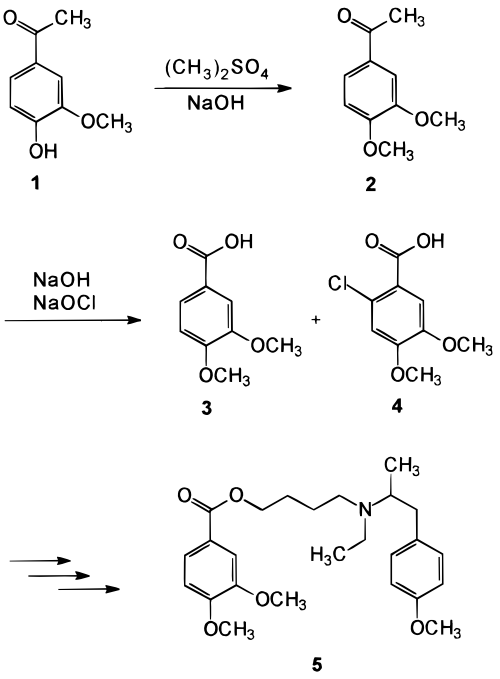
Abstract:

An optimisation study based upon experimental data obtained from multivariate statistical experimental design and modelling for the haloform reaction used for synthesis of 3,4-dimethoxybenzoic acid from 3,4-dimethoxy acetophenone is reported. It is shown how the different controllable process variables influence both the yield of 3,4-dimethoxybenzoic acid and the formation of the side product 2-chloro-4,5-dimethoxybenzoic acid. Two predictive multivariate models are derived and used to predict optimal conditions for the oxidation process. Using these models, a yield of 90% (from approximately 60%) of desired product is achieved. Moreover, the model describing the formation of the side-product can in fact also be applied to optimise a procedure for obtaining 2-chloro-4,5-dimethoxybenzoic acid in substantial quantities. One experiment showed that the side-product could be formed in a quantity of >20%.

Borregaard Synthesis is one of the world largest producers of vanillin (4-hydroxy-3-methoxy-benzaldehyde), offering vanillin from two different processes, based either on guaiacol or lignosulfonates (sulphite-spent liquor from cellulose production) as raw materials. The chemical process converting lignosulfonate into vanillin is constituted by a Cu^{2+}-catalysed air oxidation that is performed under elevated temperature and pressure in strong alkaline media[1]. The oxidation step is followed by a series of separation steps, including extraction, distillation, and crystallisation to obtain food grade vanillin. Moreover, from this process, many other useful organic fine chemicals can be isolated.

Some of the other products which are formed during the lignosulfonate oxidation process are vanillic acid, acetovanillon, guaiacol, dehydrovanillin, 5-carboxyvanillin, 5-carboxyvanillic acid, vanillyl, and vanilloyl acid. At Borregaard Synthesis acetovanillon (4-hydroxy-3-methoxy-acetophenone) **1** (Scheme 1) is isolated, since this serves as raw material in our production of 3,4-dimethoxybenzoic acid, **3** (veratric acid), a building block for synthesis of the smooth muscle relaxant mebeverin, **5**. The production process for veratric acid using acetovanillon, **1**, as raw material is constituted by a two-step synthesis starting with methylation of the free hydroxyl group of acetovanillon using dimethylsulphate in alkaline media to obtain 3,4-dimethoxy acetophenone, **2**. The second step is an oxidation based on the haloform reaction[2] with sodium hypochlorite in alkaline media to give the desired product veratric acid, **3**. The chemical process is outlined in Scheme 1.

Scheme 1



In the oxidation step, a substantial amount of a side product, 2-chloro-4,5-dimethoxybenzoic acid, **4**, may also be formed. However, by accurate control of the reaction temperature and continuous monitoring and control of the sodium hypochlorite quantity, the formation of the side product **4** can be limited. Although, the current process gives a high quality product, with a fairly good yield (55−60%), it was considered to be tedious and time-consuming, due to the need for controlled addition of the oxidation agent and substrate over a long period, with adjacent off-line analytical control experiments. This motivated us to look for an improvement and optimisation of the process. Thus, at our laboratory we have re-engineered the performance of the oxidation process, the haloform reaction, and carried out an optimisation study based upon multivariate experimental design and modelling.

Methods and Results

Experimental Variables and Domains. The objectives of the present study were as indicated above to improve the outcome and to improve the selectivity and the total

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(1) (a) Hocking, M. B. *J. Chem. Educ.* **1997**, *74,* 1055−1059. (b) Bjørsvik, H.-R.; Minisci, M. *Org. Process Res. Dev.* **1999**, *3,* 330−340.

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Table 1. **Experimental design [$2^{5-1} + 4$] with corresponding responses**

	exptl variables[a,b]					responses[c]					
						y_3			y_4		
						x_6					
						−1	0	+1	−1	0	+1
No.	x_1	x_2	x_3	x_4	x_5	1.0 h	1.5 h	2.0 h	1.0 h	1.5 h	2.0 h
1	−1	−1	−1	−1	+1	87.8	92.1	92.1	3.3	3.2	3.4
2	+1	−1	−1	−1	−1	38.9[d]	67.6[d]	68.5	14.1	15.1	15.9
3	−1	+1	−1	−1	−1	52.8[d]	79.6[d]	77.5	5.1	16.4	15.2
4	+1	+1	−1	−1	+1	68.4	62.4	62.2	17.2	13.1	16.7
5	−1	−1	+1	−1	−1	83.6	84.2	87.9	2.4	8.5	8.8
6	+1	−1	+1	−1	+1	87.3	82.8	83.2	2.7	2.6	0.0
7	−1	+1	+1	−1	+1	71.1	67.4	71.4	15.2	13.1	13.9
8	+1	+1	+1	−1	−1	81.4	77.9	75.5	2.7	8.7	13.6
9	−1	−1	−1	+1	−1	78.2	76.1	83.1	0.0	0.0	3.0
10	+1	−1	−1	+1	+1	66.6	74.0	76.2	2.9	3.0	2.9
11	−1	+1	−1	+1	+1	91.5	83.7	87.2	8.4	5.8	5.4
12	+1	+1	−1	+1	−1	72.1	77.3	79.4	17.1	19.0	19.2
13	−1	−1	+1	+1	+1	98.3	93.1	99.3	3.2	0.0	3.2
14	+1	−1	+1	+1	−1	88.5	94.9	96.7	3.8	4.1	4.1
15	−1	+1	+1	+1	−1	81.7	76.9	73.8	3.1	3.2	3.0
16	+1	+1	+1	+1	+1	82.6	86.6	80.8	3.3	3.4	3.6
17	0	0	0	0	0	80.0	80.1	79.7	6.0	4.8	5.1
18	0	0	0	0	0	82.2	84.8	86.4	2.8	3.1	2.7[d]
19	0	0	0	0	0	74.5	79.2	65.5[d]	0.0[d]	12.1[d]	0.0[d]
20	0	0	0	0	0	76.4	76.0	80.7	9.2	10.0	11.6

[a] The amount of acetoveratron in each experiment was 50 mL (56.25 g 93% to 52.3 g 100%, 0.29 mol). [b] Experimental variables: x_k (Definition) [levels: −1, 0, +1]: x_1 (start temperature/°C) [20, 35, 50]; x_2 (addition time for sodium hypochlorite/min) [5, 10, 15]; x_3 (reaction temperature/°C) [60, 75, 90]; x_4 (amount of sodium hypochlorite/mL) [350, 385, 420]; x_5 (amount of sodium hydroxide/mL 50%) [6.0, 7.5, 9.0]. [c] $y_{3,t}$ yield of veratric acid at reaction times 1.0 h, 1 h 30 min, and 2 h; $y_{4,t}$ yield of 2-chloroveratric acid at reaction times 1.0 h, 1 h 30 min, and 2 h. [d] Detected as abnormal response in the regression analyses.

performance of the synthetic process for 3,4-dimethoxybenzoic acid. During a multivariate experimental design, a critical and accurate examination of the process variables was performed in order to (i) determine which of the different variables has an influence on the formation of the veratric acid **3**, (ii) determine the detailed conditions that give maximum yield concomitant with a minimum formation of the side product 2-chloro-4,5-dimethoxybenzoic acid **4**, and (iii) simplify the process with respect to the monitoring and control requirements and thus hopefully reduce the total residence time of the process.

Before the type of experimental design was chosen, the existing process was thoroughly examined to identify and verify all of the controllable variables. The following variables were thus detected: start temperature (x_1), addition time for sodium hypochlorite (x_2), reaction temperature (x_3), amount of sodium hypochlorite (x_4), amount of sodium hydroxide (x_5), and the total reaction time (x_6). A $2^{5-1} + 4$ ($N = 20$ experiments) fractional factorial design[3] with center experiments was used. The reaction time (x_6) was also included as a controllable variable in the experimental design, since analytical samples were taken at three different times for each experiment of the experimental design (Table 1). Hence, the total number of objects in the design matrix becomes $N = 60$ experiments, which gives, in fact, the design $(2^{5-1} + 4) \times 3^1$. The experimental design with the adjacent measured responses, the chromatographic measurements, is given in Table 1. The success of the present optimisation study becomes clear only after some runs of the experimental design. Almost all of the experiments gave a higher yield than the current veratric acid process, although some significant quantities of the side product were also formed, which is detrimental for the process.

Two simple response surface models (RSM),[4,5] eq 1, were calculated, one for each of the two responses the yields of 3,4-dimethoxybenzoic acid (y_3) and 2-chloro-4,5-dimethoxybenzoic acid (y_4), respectively. The multivariate correlation, $y_N = f(x_1, x_2, x_3, ..., x_6)$, were carried out using the multiple linear regression method[6] and the partial least-squares regression (PLSR) method.[7,8] The influencing variables were determined by using the regression coefficient spectrum with estimated confidence intervals (Figure 1a,b), whereas the numerical values of the two final models [eqs 2 and 3] are given in Table 2.

$$y_N = \nu_0 + \sum_{i=1}^{6} \nu_i \times \boldsymbol{x}_i + \sum_{i=1}^{5}\sum_{j=2}^{6} \nu_{ij} \times \boldsymbol{x}_i \times \boldsymbol{x}_j, \quad i < j \qquad (1)$$

Statistical Analysis of the Models. During the introductory regression analysis for the model describing the formation of 3,4-dimethoxybenzoic acid (y_3), five abnormal objects

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(6) (a) Montgomery, D. C. an Pech, E. A. *Introduction to Linear Regression Analysis;* Wiley: New York, 1982; pp 1−504. (b) Draper, N. A.; Smith, H. *Applied Regression Analysis*, 2nd Ed., Wiley: New York, 1981; pp 1−709.

(7) Martens, H.; Næs. T. *Multivariate Calibration*, Wiley: New York, 1991; pp 116−165.

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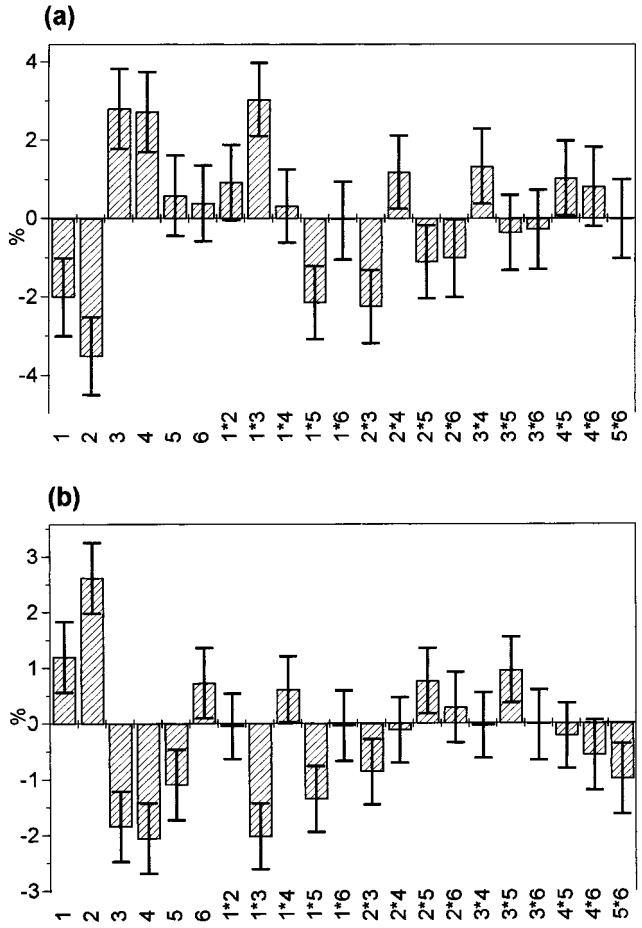

Figure 1. **The regression spectra are for scaled and centered coefficients for the models for: (a) Veratric acid, 3, a model composed by $A = 3$ PLS components. Statistics: $N = 55$ (objects 4, 5, 7, 8, and 57 are determined as outliers in the statistical analysis), $R^2 = 0.8854$, $R^2_{Adj} = 0.8413$, DF = 39, $Q^2 = 0.7611$, RSD = 3.3994, and confidence level = 0.95. (b) 2-Chloro-3,4-dimethoxybenzoic acid, 4, a model composed by $A = 2$ PLS components. Statistics: $N = 56$ (objects 54, 55, 56, and 57 are determined as outliers in the statistical analysis), $R^2 = 0.8864$, $R^2_{Adj} = 0.8512$, DF = 42, $Q^2 = 0.7943$, RSD = 2.1988, and confidence level = 0.95.**

were detected and hence excluded from the data matrixes. The abnormal objects were 4, 5, 7, 8, and 57, corresponding to entries 2 (for 1 h and 1.5 h), 3 (for 1 h and 1.5 h), and 19 (at 2 h) of Table 1.

The statistical products indicate an acceptable or good fit for the final model in eq 2. The percent of the variation of the response explained by the model is $R^2 = 0.8854$ (R^2 overestimates the goodness of fit). The predictive power of the model expressed in the same units as R^2 is $Q^2 = 0.7611$ (Q^2 underestimates the goodness of fit and is according to cross validation[9]).

$$y_3 = \alpha_0 + \alpha_1 x_1 + \alpha_2 x_2 + \alpha_3 x_3 + \alpha_4 x_4 + \alpha_5 x_5 + +\alpha_6 x_6 + \alpha_{12} x_1 x_2 + \alpha_{13} x_1 x_3 + +\alpha_{15} x_1 x_5 + \alpha_{23} x_2 x_3 + \alpha_{24} x_2 x_4 + \alpha_{25} x_2 x_5 + \alpha_{26} x_2 x_6 + \alpha_{34} x_3 x_4 + \alpha_{45} x_4 x_5 \quad (2)$$

The final model which explains the formation of the side product 2-chloro-4,5-dimethoxybenzoic acid is given in eq 3. In the introductory regression analysis, objects 54, 55, 56, and 57 were determined to be abnormal. These objects are entries 18 (at 2 h) and 19 (at 1 h, 1.5 h, and 2 h) of Table 1. The abnormal objects were removed from the data matrixes before the final modelling was performed. The statistical products, $R^2 = 0.8864$ and $Q^2 = 0.7943$, indicate also an acceptable final model, eq 3, for the side product 2-chloro-4,5-dimethoxybenzoic acid (y_4). The estimated coefficient values for the two models [eqs 2 and 3] are given in Table 2.

$$y_4 = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4 + \beta_5 x_5 + +\beta_6 x_6 + \beta_{13} x_1 x_3 + \beta_{14} x_1 x_4 + +\beta_{15} x_1 x_5 + \beta_{23} x_2 x_3 + \beta_{25} x_2 x_5 + \beta_{25} x_2 x_5 + \beta_{35} x_3 x_5 + \beta_{56} x_5 x_6 \quad (3)$$

The two models were used to estimate the response surfaces of Figure 2 a,b. On the basis of these two response surfaces the conditions for two more experiments were predicted. The goals of these two experiments were (i) to obtain a high yield of veratric acid **3** without formation of the side product **4** (entry 1 of Table 3) and (ii) to obtain a "maximised" yield of the side product 2-chloro-4,5-dimethoxybenzoic acid, **4** (entry 2 of Table 3). The only goal of this experiment was to check the predictive capability of the model of eq 3. The conditions for these two experiments of Table 3 were selected from the explored experimental domain, in such a way that the expected yield of veratric acid **3** was >95% concomitant with the near absence of the undesired side product 2-chloro-4,5-dimethoxybenzoic acid, **4**.

Discussion and Conclusion

Chemical Interpretation of the Models. To obtain a high yield of 3,4-dimethoxybenzoic acid, **3**, it is beneficial to (i) apply a rather low temperature in the reaction medium in the initiation of the reaction, (ii) apply a short addition time, (iii) use a high reaction temperature, (iv) add a large excess of sodium hypochlorite, (v) add an excess amount of sodium hydroxide, and (vi) use a short to medium-long reaction time. All of the statements (i−vi) above refer to the explored experimental domain as given in Table 1.

However, these conclusions are only general interpretations for each of the single experimental variables. In addition to these general considerations, the two-variable interactions for the regression coefficients α_{12}, α_{13}, α_{15}, α_{23}, α_{24}, α_{25}, α_{26}, α_{34}, and α_{45} were also determined to have significant influence on the formation of veratric acid, **3**. All of these two-variable interactions imply that the interpretation of the empirical mathematical model becomes more difficult. However, by using a multidimensional response surface, a good understanding of how the response varies with the different controllable variables becomes clear. Figure 2a,b shows the four-dimensional response surfaces for veratric acid, **3**, and 2-chloro-4,5-dimethoxybenzoic acid, **4**, respectively. These two response surfaces were used to select conditions which give a high yield of veratric acid, **3,** with an adjacent low yield of the side product 2-chloro-4,5-dimethoxybenzoic acid, **4**. The results of these two experi-

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Table 2. **Estimated model parameter values for eqs 2 and 3**

model parameters for y_3[a]					model parameters for y_4[b]				
coef./value		SEM	P	conf. int. ±	coef./value		SEM	P	conf. int. ±
α_0	80.92	0.47	0.00	0.94	β_0	7.29	0.29	0.00	0.59
α_1	−1.99	0.48	0.00	0.97	β_1	1.21	0.30	0.00	0.60
α_2	−3.5	0.47	0.00	0.96	β_2	2.63	0.30	0.00	0.60
α_3	2.89	0.48	0.00	0.97	β_3	−1.85	0.30	0.00	0.60
α_4	2.69	0.48	0.00	0.96	β_4	−2.06	0.30	0.00	0.60
α_5	0.65	0.48	0.18	0.97	β_5	−1.10	0.30	0.00	0.60
α_6	0.25	0.47	0.60	0.95	β_6	0.74	0.30	0.02	0.60
α_{12}	0.93	0.44	0.04	0.89	β_{13}	−2.03	0.28	0.00	0.56
α_{13}	3.09	0.44	0.00	0.89	β_{14}	0.62	0.28	0.03	0.56
α_{15}	−2.09	0.44	0.00	0.89	β_{15}	−1.37	0.28	0.00	0.56
α_{23}	−2.21	0.44	0.00	0.89	β_{23}	−0.88	0.28	0.00	0.56
α_{24}	1.19	0.44	0.01	0.89	β_{25}	0.77	0.28	0.01	0.56
α_{25}	−1.10	0.44	0.02	0.89	β_{35}	0.96	0.28	0.00	0.56
α_{26}	−1.00	0.47	0.04	0.96	β_{56}	−1.02	0.30	0.00	0.60
α_{34}	1.27	0.44	0.01	0.88					
α_{45}	1.00	0.44	0.03	0.88					

[a] Statistical products for the model describing the formation of veratric acid (PLS components = 3) are $N = 55$, $R^2 = 0.885$, $Q^2 = 0.761$, $R^2_{Adj} = 0.8413$, RSD = 3.3994, confidence level = 0.95. [b] Statistical products for the model describing the formation of the 2-chloro-3,4-dimethoxybenzoic acid (PLS components = 2) are $N = 56$, $R^2 = 0.886$, $Q^2 = 0.794$, $R^2_{Adj} = 0.8514$, DF = 42, RSD = 2.199, confidence level = 0.95.

Table 3. **Optimisation experiments carried out on basis of the derived models for veratric acid and 2-chloro-3,4-dimethoxybenzoic acid, respectively**

	exptl variables[a]						observed/predicted responses[b]			
no.	x_1	x_2	x_3	x_4	x_5	x_6	$y_{obs(3)}$	$y_{pred(3)}$	$y_{obs(4)}$	$y_{pred(4)}$
1	20	5	70	430	9	60	88.5	95.6	nd	−1.3
						90	86.0	95.6	nd	−1.7
						120	90.8	95.8	nd	−2.0
2	40	25	40	290	6	60	61.4	72.2	20.3	37.8
						90	53.3	74.0	18.1	39.6
						120	51.6	75.5	17.6	41.4
3[d]	20	5	70	430	4.5[e]	15	86.6		nd	
						30	90.5		nd	
						60	91.7		nd	

[a] The amount of acetoveratron in each experiment was 43 g (0.24 mol). [b] Experimental variables: x_k (definition): x_1 (start temperature/°C); x_2 (addition time for sodium hypochlorite/min); x_3 (reaction temperature/°C); x_4 (amount of sodium hypochlorite/mL); x_5 (amount of sodium hydroxide/mL 50%), x_6 (reaction time/min). [c] $y_{obs(3)}$ observed (measured) yield of veratric acid, $y_{pred(3)}$ predicted (calculated) yield of veratric acid, $y_{obs(4)}$ observed (measured) yield of 2-chloroveratric acid $y_{pred(3)}$ predicted (calculated) yield of 2-chloroveratric acid. [d] The experiment was performed with inverse addition; the acteoveratrone was added to a solution composed by sodium hydroxide and sodium hypochlorite. [e] Sodium hydroxide pellets (4.5 g) were dissolved in water (9 mL). nd = not detected.

ments are given in Table 3, where entry 1 shows the success of the re-engineered and optimised oxidation process, giving a yield of ~91%, while the chlorinated side product **4** is not detected. Moreover, entry 2 of Table 3 shows the results of the optimised side product reaction, which confirms the predictive ability of the model, eq 3. Furthermore, the optimised procedure was also tried in an inverse addition experiment, entry 3, Table 3. From a process point of view, addition of the acetoveratrone to the oxidation agent is a better way to perform the process, because (i) the volume of the oxidation agent is much larger than the volume of the substrate (acetoveratrone), a volume ratio of approximately 9:1. (ii) the addition time of the oxidation agent, according to the model, eq 2, should be very short, which would require a pump of very high capacity. The inverse addition experiment was successfully carried out to obtain a yield of approximately 92% of the veratric acid (measured in the reaction mixture), while the chlorinated side product was not detected. Expected isolated yield is approximately 65−70%.

As can be seen from the response surfaces of Figure 2 a,-b, many combinations of the experimental variables may give a high yield of veratric acid, **3**, concomitant with a zero level of the side product **4**. Thus, establishing such response surfaces can give rise to further optimisation of the process. The economical aspects of the process can also be included, for example, by selecting the expensive variables to be as low as possible, or by selecting them in such a way that the optimal use of the process equipment is obtained. Moreover, process development using statistical experimental design and modelling also gives very good possibilities for cost and time estimation of process development work.

Experimental Section

General Synthetic Procedure. Acetoveratron (Borregaard Synthesis) (50 mL, 0.24 mol) and sodium hydroxide (Borregaard) (50%, 6 or 9 mL) were mixed using a mechanical strirrer with a speed of 430 rpm. The mixture was heated to a start temperature of 20 or 50 °C. Sodium

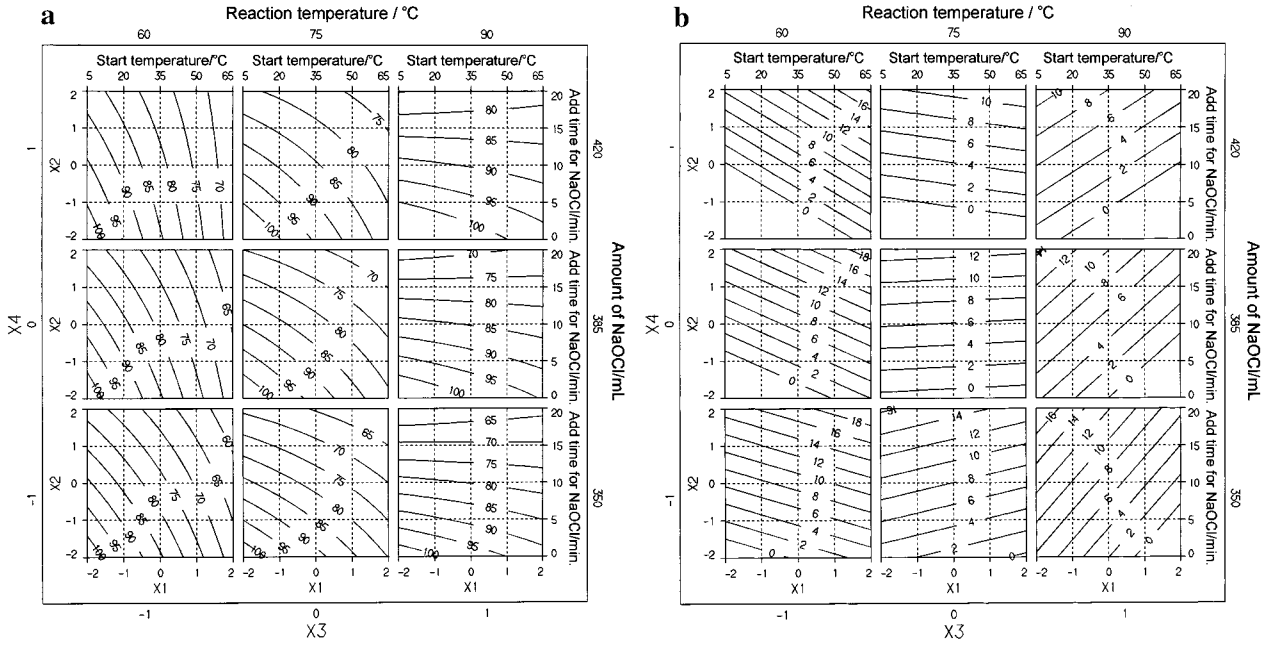

Figure 2. **(a) Response surface projections of eq 2, the model which describes the formation of veratric acid. The contour lines show the yield of veratric acid, 3, when the four experimental variables (x_1 the start temperature/°C, x_2 addition time for sodium hypochlorite/min, x_3 reaction temperature/°C, and x_4 amount of sodium hypochlorite/mL) are varied. The two experimental variables x_5 (amount of sodium hydroxide/mL 50%) and x_6 (reaction time/h) are kept at the fixed levels $x_5 = +1$ (9 mL) and $x_6 = +1$ (2 h). To read the plot, the large frame shows the variation in the reaction temperature/°C (x_3) and in the amount of sodium hypochlorite/mL (x_4). In this frame nine subplots showing the contour lines of the response surface when the experimental variables start temperature/°C (x_1) and the addition time for sodium hypochlorite/min (x_2) are varied. (b) Response surface projections of eq 3, the model which describes the formation of 2-chloro-3,4-dimethoxybenzoic acid. The contour lines show the yield of 2-chloro-3,4-dimethox benzoic acid 4 when the four experimental variables x_1 the start temperature/°C, x_2 addition time for sodium hypochlorite/min, x_3 reaction temperature/°C, and x_4 amount of sodium hypochlorite/mL are varied. The two experimental variables x_5 amount of sodium hydroxide/mL 50% and x_6 reaction time/h are kept at the fixed levels $x_5 = +1$ (9 mL) and $x_6 = +1$ (2 h). To read the plot, the large frame shows the variation in the reaction temperature/°C (x_3) and in the amount of sodium hypochlorite/mL (x_4). In this frame nine subplots showing the contour lines of the response surface when the experimental variables start temperature/°C (x_1) and the addition time for sodium hypochlorite/min (x_2) are varied.**

hypochlorite (Borregaard Synthesis) (2.26 M, 350 or 420 mL) was then added over a period of 5 or 15 min, and the reaction temperature was increased to 60 or 90 °C for the rest of the reaction time (2 h). Samples of the reaction mixture were withdrawn at 1 h, 1.5 h, and 2 h. The variation and combination of the different settings for the experimental procedures are given in Table 1.

Sample Preparation. The withdrawn sample (approximately 20 g) was weighed accurately and quenched with sodium bisulphite. The pH of the quenched sample was then adjusted using sulphuric acid (Merck) to obtain a pH of 3−4. The acidified solution was extracted with dichloromethane (Merck) (50 mL, 2 × 15 mL). The dichloromethane extracts were combined and transferred to a volumetric flask (100 mL). The internal standard (125 mg of guaiacol) was then added and the mixture diluted to the mark with more dichloromethane. A sample (1 mL) was withdrawn and derivatized by using a mixture of pyridine (Merck)/hexamethyldisilazane (Scanlab)/trimethylsilyl chloride (Scanlab) (10:2:1) in a ratio 2:1 (sample/derivatization reagent). A sample (1 μL) was injected on the GC.

NMR of the side product 2-chloro-4,5-dimethoxybenzoic acid: ^{1}H NMR (d_6-DMSO): δ 13.086 (s, 1H, COO*H*); 7.381 (s, 1H, aromatic H_a); 7.077 (s, 1H, aromatic H_b); 3.842−3.798(6H 2·CH_3).

^{13}C NMR (d_6-DMSO): δ 165.927 (*C*OOH); 151.623 (C_q, *C*−CO); 147.041 (C_q−Cl); 125.047; 121.633 (C_q−OCH_3); 113.708, 113.601 (aromatic *C*−H); 56.010; 55.668 2·CH_3).

GC Chromatograpic method: column, 10% SP 2100 (packed); injector temperature 250 °C; programme, 140 °C for 15 min, 140−250 °C at 10 °C/min, 250 °C for 39 min; solvent, dichloromethane; flow rate N_2, 22.5 mL/min.

Optimised Synthetic Procedures. *Optimised Procedure Based on the Experimental Design Procedure.* Acetoveratrone (Borregaard Synthesis) (50 mL, 0.29 mol) and sodium hydroxide (50%, 9 mL) were mixed using a strirring speed of 430 rpm. The mixture was heated to a temperature of 20 °C. Then, sodium hypochlorite (Borregaard Synthesis) (2.26 M, 430 mL) was added over period of 5 min. The reaction temperature was then increased to 70 °C for the rest of the reaction period, 2 h. Expected yield of veratric acid in the reaction mixture is 91 w/w % and the side product is not detected.

Inverse Addition Experiment. Sodium hydroxide (4.5 g, 0.1125 mol) was dissolved in water (9 mL) and added to a solution of sodium hypochlorite (Borregaard Synthesis) (2.26 M, 430 mL) which was placed in a 1-L reactor. The solution was stirred with a mechanical stirrer (430 rpm) at a temperature of 20−21 °C. Acetoveratrone (Borregaard Synthesis) (48.87 g, 88.6% pure, 0.24 mol) was then added

over a period of 5 min. Due to the exothermic reaction between acetoveratrone and the hypochlorite, the temperature rose to 24−25 °C. The reaction mixture was heated further to a temperature of 70 °C. The reaction mixture was analysed after 15 min, 30 min, and 1 h. Expected yield of veratric acid in the reaction mixture is 92 w/w % and the side product is not detected.

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