Organic Process Research & Development **2004**, *8,* 1036–1041

Synthetic Process Development and Scale-Up of the Oxidative Cleavage of a Double Bond Catalyzed by Ruthenium Trichloride

Wilhelm Quittmann, Dominique M. Roberge, and Yves Bessard*

Department of Process Research, Lonza Ltd., P.O. Box CH-3930 Visp, Switzerland

Abstract:

Using statistical experimental tools, a relatively complex process for the oxidative cleavage of a double bond catalyzed by a ruthenium catalyst was studied. A good understanding of the influence of the reaction parameters led to the development of a technically feasible process which was successively scaled up to kilogram-laboratory facilities and finally to the launch plant facilities.

Introduction

In the course of a recent process development project we were confronted with a frequently occurring problem: how to minimize the formation of several side products without negatively affecting the yield and the throughput of the reaction?

The process consists of a two-step reaction where a conjugated double bond of a cyclic α,β-unsaturated ketone is oxidatively cleaved and the resulting keto acid is then cyclized to a lactam without isolation.

The majority of the impurities are formed during the oxidation step. For practical and economical reasons, the intermediate is not isolated and thus is not purified.

The impurities are consequently present in the cyclization step and can either remain unaffected or react further at this stage. The main impurities, having structures similar to those of the desired product, also have similar properties and can only be removed with difficulty from the product without incurring losses.

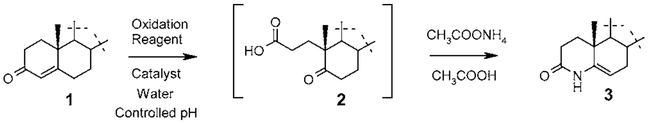
An extended study of the parameters was undertaken, leading to a good understanding of the process. However, fine-tuning was necessary to get a very robust process, since the specifications for the side products present in the final product were set at a low level.

Statistical experimental design[1] proved to be the most appropriate tool to answer our questions. For this purpose, the data generated was analyzed with the software Modde from Umetrics.[2]

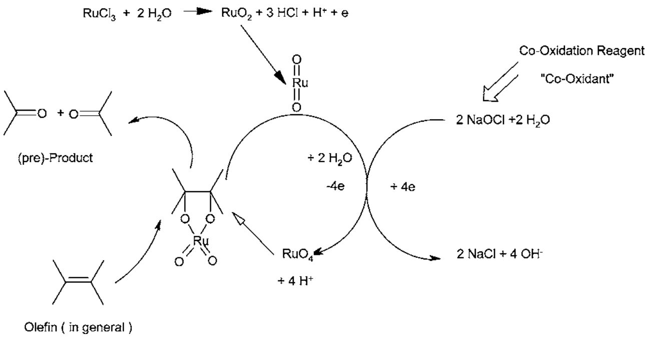
Chemistry

An important point to be decided before starting an optimization is to select the preferred chemical transformation. Thus, several ideas were generated during brainstorming sessions; some of these ideas have been investigated, and finally, the route presented in Scheme 1 was found to be the most suitable for our purpose and was therefore developed.

Scheme 1. **Preferred reaction sequence**



Scheme 2. **Oxidation reaction mechanism**



The unsaturated ketone **1** is oxidized with sodium hypochlorite using a catalytic amount of ruthenium (III) trichloride under carefully controlled pH conditions by simultaneous addition of sodium hydroxide. After treatment of the reaction mixture with sodium hydrogen sulfite and then acidification with hydrochloric acid, the resulting keto acid **2** is extracted with ethyl acetate. Finally the solvent is exchanged with acetic acid, and the resulting mixture is used in the following step.

The cyclization reaction is carried out under mildly acidic conditions with ammonium acetate to afford the corresponding lactam **3**. The precipitation of the product occurs during the reaction. The crystallization is completed by addition of water, and the product is isolated by centrifugation.

Most of the 10−12 impurities present with the intermediate **2** disappear during the isolation of the product **3**. Nevertheless three critical impurities are always present in the final product at levels of up to 1%, depending on the reaction conditions. These impurities are essentially over-oxidized side products (SP1, SP2, and SP3), and their level remains practically unaffected by the purification process.

The applied oxidation reaction mechanism[3] is outlined in Scheme 2.

---

* To whom correspondence should be addressed. Telephone: (41) 27 948 5800. Fax: (41) 27 948 6180. E-mail: yves.bessard@lonza.com.

(1) Owen, M. R.; Luscombe, C.; Lai, L. W.; Godbert, S.; Crookes, D. L.; Emiabata-Smith, D. *Org. Process Res. Dev.* **2001**, *5*, 308 and 324.

(2) Erikson, L.; Johansson, E.; Kettaneh-Wold, N.; Wikström, C.; Wold, S. *Design of Experiments, Principles and Applications*; Umetrics AB: Umeå, 2000.

(3) Kaneda, K.; Harana, S.; Imanaka, T.; Kawamoto, K. *J. Chem. Soc., Chem. Commun.* **1990**, 1467.

10.1021/op040014f CCC: $27.50

Alternative co-oxidation reagents for ruthenium dioxide such as $NaIO_4$ in t-BuOH/H_2O solvent system to oxidize the olefinic double bond in steroids are described in the literature.[4] Due to the high price of periodates, bleach is usually preferred as an oxidation reagent.

Potassium permanganate[5] is the classical oxidation reagent in the steroid series and also for terpenes and terpenoids, but it must be used at least in stoichiometric amount. It was not applied in this case as yields obtained with potassium permanganate seldom exceed 50%. Associated problems with waste management are also to be expected.

It was not necessary to look for alternatives to the cyclization step as this methodology is known to produce azasteroids.[6,7]

The Targets

At this point it was important to clearly define which goals we wanted to reach. In our case study it was quite clear that our targets were the following:

(a) **product quality**, to meet the specifications,

(b) **efficiency**, by getting the highest possible yield (best possible conversion), and

(c) **costs**, by getting the highest possible throughput.

The highest yields were always obtained by full conversion of our very expensive starting material **1**, but the full conversion could only be obtained by adding an excess of oxidation reagent, resulting in a high level of side products.

The highest throughput was obtained when the reaction was carried out at high concentration, also resulting in high levels of side products.

One can quickly notice that for each of the required targets, opposite results would be obtained when the parameters were individually optimized.

Methodology of Parameter Optimization

It has to be decided now which strategic approach should be followed to reach our goals, either a more traditional approach or a statistical experimental design. Both approaches were found useful to our study in the following ways:

(a) The traditional approach, single-parameter study, was first used to increase familiarity with the process. An early phase RC-1 experiment was also performed to obtain as much information as possible in one single experiment with the advantage of identifying critical parameters.[8]

(b) The experimental design was used afterwards to generate a response surface model (RSM) of different responses and to determine how robust the system is, close to the maximum.

Early Phase RC-1

Due to the complexity of the process, a thorough evaluation of all the potential parameters was therefore necessary. Once all the potential parameters have been taken into account, the way forward is to group the variables into categories such as those known to influence, suspected to influence, and suspected not to influence. Then, on the basis of preliminary experiments and common sense one may reduce the number of parameters.

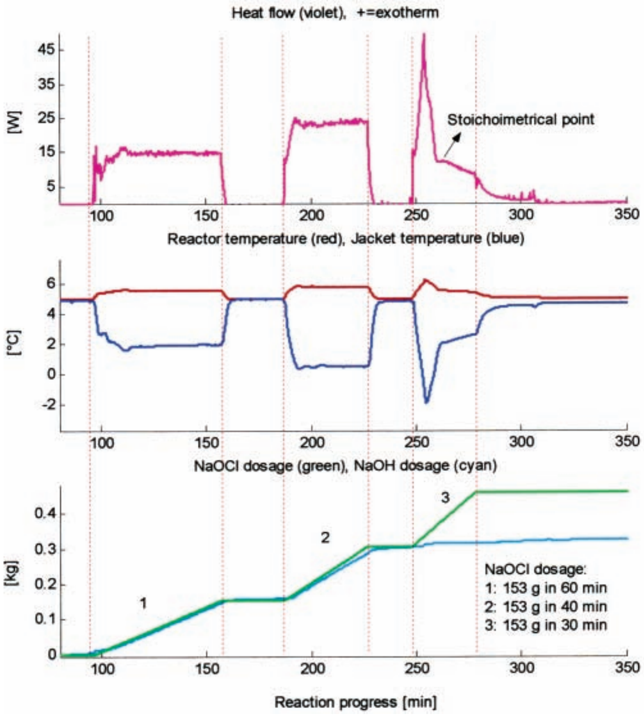


Figure 1. **RC-1 evaluation of the reaction with initial conditions.**

Another strategy developed within Lonza to identify critical parameters is to perform an early phase RC-1 experiment.[8] Figure 1 shows the typical trends obtained after performing such an RC-1 experiment with reaction conditions chosen initially by experience of the chemist. Very useful information is generated by following a certain RC-1 methodology.

First of all one will observe that the sodium hypochlorite solution has not been dosed in one step but subdivided into three steps with three different dosage speeds. The heat signal in watts increases proportionally to the dosage speed; the reaction is indeed completely dosage controlled (at the third dosage the maximum heat flow is considered to occur just before the sharp fall of the heat flow). The reaction rate is analyzed during one of the intermediate dosage interruptions before the stoichiometric point has been reached. In this case, one can observe two very clear rectangular boxes with no indication of accumulation. It is important not to use the accumulation at the end of the dosage as an indication of the reaction speed. The reaction has been performed with an excess of NaOCl (5.2 equiv, theoretically 4.0 equiv), and this accumulation may account for the overoxidation of the product. Within the limits of the RC-1 sensitivity, we would now consider this reaction to be complete in less than 3 min. It would be classified as a rapid reaction having high potential for mass transfer limitations.[8] This aspect is further amplified

---

(4) Rasmusson, G. H.; Reynolds, F. G.; Steinberg, N. G.; Walton, E.; Patel, F. G.; Liang, T.; Cascieri, M. A.; Cheung, A. H.; Brooks, J. R.; Berman, C. *J. Med. Chem.* **1986**, *29*, 2298.

(5) Amos, A. A.; Ziegler, P. *Can. J. Chem.* **1960**, *38*, 1130.

(6) Uskokovic, G. *Helv. Chim. Acta* **1959**, *42*, 2258.

(7) Guarna, A.; Occhiato, E. G.; Machetti, F.; Scarpi, D. *J. Org. Chem.* **1998**, *63*, 4111.

(8) Roberge, D. M. *Org. Process Res. Dev.* **2004**, *8*, 1049.

by the fact that the main reactant is a suspended solid in an aqueous solution.

The sharp reduction of the heat signal close to the stoichiometrical point is a good indication of the very rapid nature of the main reaction. The remaining heat signal may then be caused by other oxidation pathways. Moreover, the thermally neutral behavior of the system after the addition of $NaHSO_3$ (results not shown here) shows that no excess oxidant is present and the excess hypochlorite is rapidly consumed at the end of the reaction. Nevertheless, the addition of $NaHSO_3$ is a critical step to ensure that RuO_4 has been reduced to a lower oxidation level and that potential peroxides have been destroyed.

From these results, it appears that the scale-up effect is something that must be addressed during process development and not just when the process is ready to be transferred into production. Moreover, parameters such as stoichiometry (reactant relative to oxidant), reactant concentration, and pH are critical.

Scale-Up Considerations

The parameters that are now suspected to influence the outcome of the reaction, such as dosage speed, reagent particle size, agitation, and amount of catalyst, become critical if the reaction is mass transfer limited. The reaction has a strong potential to be solid−liquid mass transfer limited because the key starting reagent is only slightly soluble (solubility of 0.8 wt %) and remains as a suspended solid in the reaction medium. At this point of the work it was debated whether a laboratory reactor geometrically equivalent to the one that would be used in production should be used for laboratory work to get reproducible results on scale-up. A simple scale-up analysis enabled us to gain a better understanding of those parameters.

If we assume that the reaction is fully mass transfer limited (solid to liquid), then a relation exists between the Sherwood (Sh), Schmidt (Sc), and Reynolds (Re) number:[9]

$$\mathrm{Sh}\cdot\mathrm{Sc}^{-0.5} = \mathrm{Re}^{0.58}$$

By building a ratio of the above-mentioned equation with plant (subscript 2) and laboratory (subscript 1) dimensions, one obtains after rearrangement the following equation:

$$\frac{k_{L1}}{k_{L2}} = \left(\frac{n_1}{n_2}\right)^{1.08}\left(\frac{d_1}{d_2}\right)^{1.16}$$

where k_L represents the mass transfer coefficient, n the stirrer speed, and d the stirrer diameter. By assuming geometric similarities and taking into account that in the plant $d_2 = 700$ mm and $n_2 = 120$ rpm, the stirrer speed required to obtain the same k_L value on laboratory scale (assuming $d_1 = 48$ mm) would be around 2130 rpm. One can see that this stirrer speed is unrealistic due to strong vortex formation that would arise. It was concluded that on typical laboratory scale, with reactor size of less than 1 L, unscalable results would be obtained if the reaction is highly mass transfer limited. This is one of the reasons why scale-up studies should be conducted in reactors of at least 20 L. Nevertheless, it may be concluded that mixing conditions in terms of k_L (solid−liquid mass transfer coefficient) obtained in production would be more favorable than conditions obtained in the laboratory with a stirrer speed at around 1000 rpm.

The initial starting material **1** proved to be very sensitive to agitation and catalyst amount. The control of the granularity by micronization of the poorly soluble starting material proved to be essential for the improvement of the reaction selectivity. Once the starting material had been micronized it remained mainly insensitive to agitation and catalyst amount. Under such conditions, both parameters could be considered as noncritical. By micronization, the reaction was found to have shifted from a mass transfer limited reaction to a kinetically controlled one. Under such conditions the geometric aspects of the reactor did not play a major role.

As the exact borderline between mass transfer limitations and kinetic control was not known and limited resources were available for the project, a conservative setting of other variables using common sense was applied. The temperature was set at low values close to the freezing point of water (5 °C) to ensure that the reaction did not accelerate enough to fall again in mass transfer limitations. A minimum of 4 h dosage time was calculated to maintain the system in an isothermal state by knowing the heat transfer coefficient in production and the minimum temperature that the cooling fluid can reach ($T_{\text{cooling}} = -15$ °C).[10]

Design of Experiments

Factors. This methodology allowed us to successively reduce the number of parameters to the most critical ones, in view of the limited time and resources available for the study. A response surface model which includes the remaining critical factors is useful in production because the model will be consistent with the laboratory results. Not having taken such scale-up aspects into account would have been a mistake for the model. On the basis of the good knowledge of the reaction parameters gained during the study following the traditional approach, we were able to reduce the main oxidation step to only three important factors:

- concentration of the reaction [water] defined by the volume in mL (300−600 mL),
- amount of oxidation reagent [NaOCl] defined as the amount of sodium hypochlorite in equivalence (3.6−4.4 equiv), and
- pH during the oxidation reaction (7.7−8.9).

The preliminary studies provided enough information to confidently select an appropriate working range for the critical parameters.

Responses. This is an important point to prove that the goals defined earlier have been actually reached. In our case study, five responses were measured:

- yield of keto acid (to be maximized),
- level of side product (1) [SP1] in the final product (below a 0.10% limit),

---

[9] Zlokarnik, M. *Stirring, Theory and Practice*; Wiley-VCH: Weinheim, 2001.

[10] Choudhury, S.; Utiger, L.; Riesen, R.; Mettler Toledo Publication 00724218, Mettler-Toledo AG, Switzerland (can be accessed at http://www.rxeforum.com).

Table 1. **Experimental matrix with results**

water [mL]	NaOCl [equiv]	pH [−]	yield [%]	SP1 [%]	SP2 [%]	SP3 [%]	SM [%]
300	3.6	7.7	77.7	0.072	0.000	0.000	2.403
600	3.6	7.7	77.1	0.050	0.040	0.000	2.203
300	4.4	7.7	79.9	0.416	0.151	0.133	0.159
600	4.4	7.7	80.3	0.197	0.116	0.093	0.123
300	3.6	8.9	75.3	0.047	0.000	0.000	0.000
600	3.6	8.9	75.1	0.000	0.000	0.000	0.000
300	4.4	8.9	73.8	0.212	0.083	0.073	0.000
600	4.4	8.9	73.6	0.139	0.058	0.043	0.000
450	4.0	8.3	79.8	0.073	0.041	0.000	0.000
320	4.0	8.3	79.5	0.065	0.036	0.000	0.000
580	4.0	8.3	79.9	0.077	0.043	0.000	0.000
450	3.7	8.3	78.1	0.040	0.000	0.000	0.121
450	4.3	8.3	78.8	0.157	0.086	0.064	0.000
450	4.0	7.8	80.0	0.131	0.064	0.041	0.228
450	4.0	8.8	75.3	0.061	0.000	0.000	0.000
450	4.0	8.3	80.0	0.074	0.034	0.000	0.000

- level of side product (2) [SP2] in the final product (below a 0.10% limit),
- level of side product (3) [SP3] in the final product (below a 0.10% limit), and
- level of unreacted starting material [SM] (should be as low as possible).

Experimental Matrix. To minimize the number of experiments and obtain a powerful response surface model, a central composite design was chosen. The design had the characteristic of being face centered, so that the high and low limits of the experimental values were not extrapolated outside of their limits. Table 1 shows in detail the setting of all factors and the corresponding responses. One will observe that 16 runs have been performed including two center points.

For the design, the experiments have been carried out in the most reproducible way possible, following the process strictly according to a careful schedule of the experiments (order of the experiments, identity of the operators, etc.). To minimize systematic errors, the reactions were conducted in random order. The two "center point" experiments were placed in the middle and at the end of the study.

Results

Table 1 shows the responses obtained in combination with their factor setting. Before looking at the detail of the models for the different responses, one can have a look at the raw data first. For all responses, an excellent reproducibility is obtained (repeated experiment at the center point). Under such conditions a good R^2 is expected.

Figure 2 shows the five most important correlations of the system before any model is applied. It can be observed that SP1, SP2, and SP3 correlate strongly together. Their formation may possibly proceed by a related mechanism. In such a case, the trend for SP1 is very similar to the trends of SP2 and SP3, and thus the response surface areas for SP2 and SP3 are not presented in this article.

Another important correlation is the one between the formation of side products and NaOCl concentration. This aspect will be discussed later.

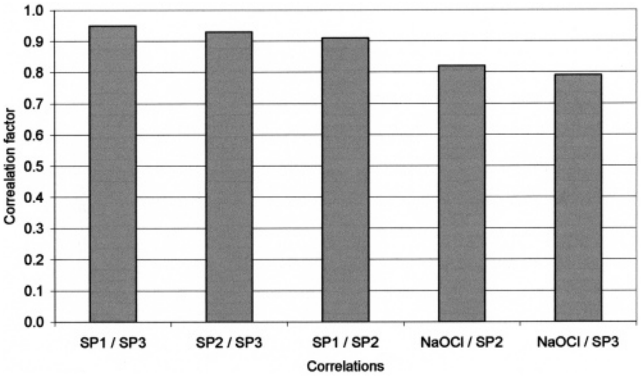


Figure 2. **Five most important correlations.**

The basic model used to fit the data is a quadratic equation with 10 terms, including one constant, three linear, three quadratic, and three two-factor interactions terms. The basic model is optimized by eliminating terms that are not relevant for the model. The approach was to optimize the predictability of the model (Q^2 as defined in Modde). Insignificant terms were removed from the model until the highest predictability was obtained. Moreover, three different models were determined for yield, SM, and SP1 and analyzed in the first instance separately. The equations, as well as their R^2 and Q^2 values are presented below. Figures 3−5 show the response surface area obtained from these models.

$$\text{yield} = -562 + 37.1 \times \text{NaOCl} + 140.0 \times \text{pH} - 7.60 \times \text{pH}^2 - 4.34 \times \text{NaOCl} \times \text{pH} \quad (R^2 = 0.96;\ Q^2 = 0.93)$$

$$\text{SM} = 144 - 48.6 \times \text{NaOCl} - 9.91\ \text{pH} + 3.59 \times \text{NaOCl}^2 + 2.25 \times \text{pH}^2 \quad (R^2 = 0.93;\ Q^2 = 0.87)$$

$$\text{SP1} = 3.59 - 0.000120 \times \text{H}_2\text{O} - 1.76 \times \text{NaOCl} - 0.0384 \times \text{pH} + 0.244 \times \text{NaOCl}^2 \quad (R^2 = 0.93;\ Q^2 = 0.87)$$

Initially, it was possible to find only a moderately good model for SP1 ($R^2 = 0.87$ and $Q^2 = 0.60$). Looking at the replicated plot of the SP1 data, it was observed that only one point had a large value (SP1 = 0.416), while all the points had a value close to and lower than 0.2. Moreover, when the experimental data for the response SP1 was analysed in detail, one strong outlier was found (Modde *N*-probability versus deleted studentized residuals). It was then decided to remove this value (SP1 = 0.416) from the experimental design, and a clear improvement in Q^2 was obtained. In conclusion, three independent models were obtained showing good R^2 and Q^2. None of the models demonstrated significant lack of fit. Thus, the models are very useful to predict the chemical behavior of the system.

With an excess of NaOCl, the conversion of starting material **1** is always complete, but isolated yields are not significantly higher (Figures 3 and 4). However the level of all impurities increases in proportion to a level which is rapidly outside the specifications (Figure 5). With a substoichiometric amount of NaOCl yields are not significantly lower (Figure 3). It is expected to have an increase of the amount of unreacted starting material **1**, but it is possible to minimize this effect by working at higher pH.

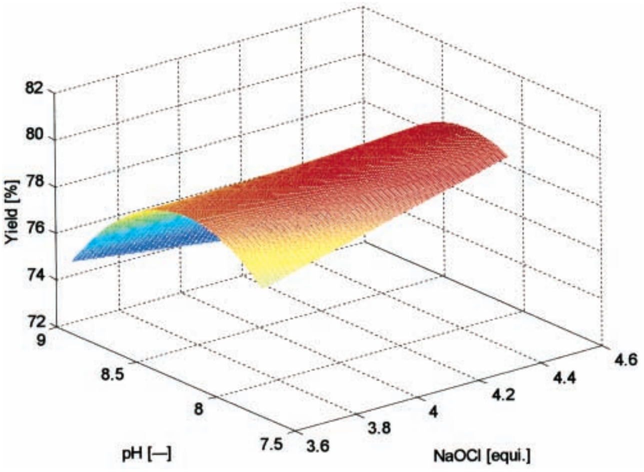


Figure 3. **Response surface model for the yield.**

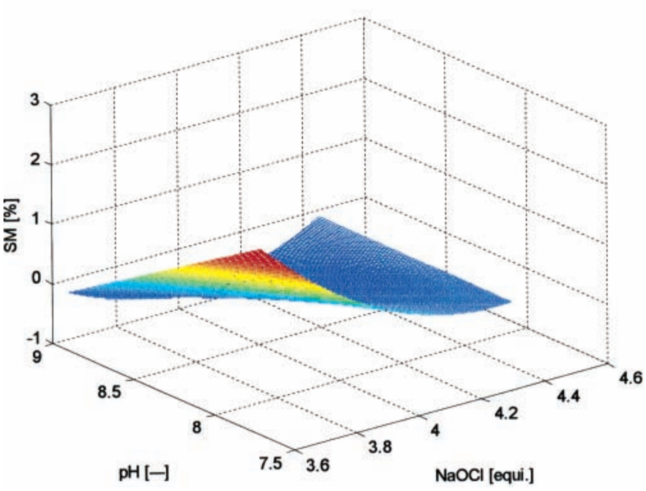


Figure 4. **Response surface model for the starting material (SM).**

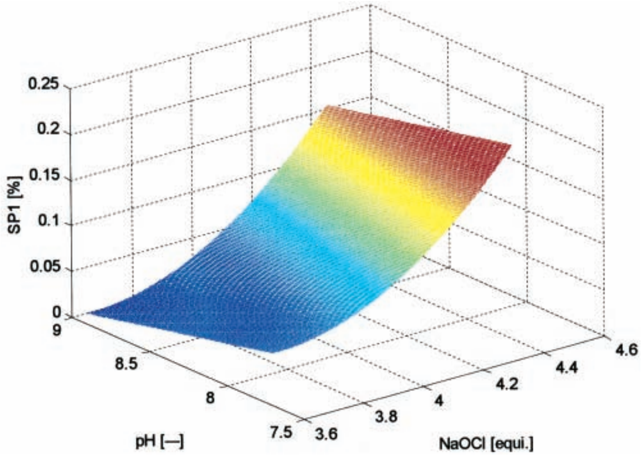


Figure 5. **Response surface model for the side product one (SP1) at H_2O = 510 mL.**

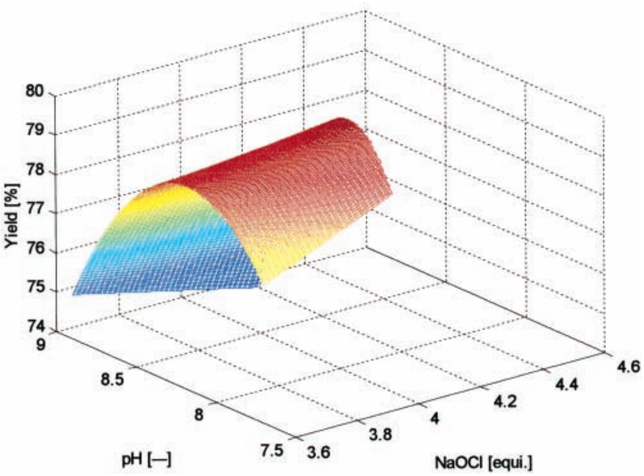


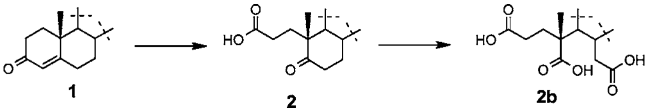
Figure 6. **Response surface model for the corrected yield (see text).**

Table 2. **Optimal reaction conditions from the model**

parameters	optimal
(1) water vol[a]	510 mL
(2) NaOCl quantity	3.90 equiv
(3) pH (reaction)	8.4

[a] Normalized for 100-mmol scale reaction.

Scheme 3. **Subsequent reaction at high pH**



The concentration is not critical as long as the other two critical parameters (NaOCl, pH) are set within their optimal range. If this is not the case, we observe an increase in the level of the side products at higher concentration.

We always notice a higher level of impurities at a pH lower than the optimal pH range. At pH values above the optimal pH range, material within specifications can be obtained, as long as the two other parameters (NaOCl, concentration) are set within their optimal range. However, at pH > 9, there is a drastic drop of the yield due to a consecutive oxidation/degradation of the intermediate **2**, as shown in the reaction schema below (Scheme 3). Formation of the enolate of intermediate **2** at higher pH values is assumed to lead to degradation of the second ring.

As mentioned earlier, the responses have clear opposing tendencies. To overcome this problem a new response surface area was modeled by taking into account the following assumptions: (a) The yield must be maximized, and (b) SP1, SP2, and SP3 must remain in all cases less than 0.10%. This is done in Figure 6 where the yield is plotted in regions where the amount of side product is less than 0.10%. No rules were defined for SM due to the fact that it is indirectly taken into account by maximizing the yield. Moreover, this starting material is almost completely removed during the crystallization and causes no additional problems that must be translated into rules. Figure 6 can now be used to read and define the optimal reaction conditions as shown in Table 2. These conditions were taken as standard operating conditions for the process. It is worth mentioning that the operating conditions were not chosen directly at the upper yield border, but toward the centre of the maximum to minimize the potential side product formation and ensure process robustness. In conclusion, under such conditions a yield of 78% is

Table 3. **Experiments schedule and results (laboratory scale)**

Reaction Parameters			
batch	water vol [mL]	NaOCl [equiv]	pH (reaction)
1, 2, 3	510	3.9	8.4

Responses					
run	yield	SP1	SP2	SP3	SM
1	78.6	0.00	0.00	0.00	0.00
2	79.4	0.00	0.00	0.00	0.00
3	[54.5]	0.00	0.00	0.00	0.00

Table 4. **Reactions conditions and results (kilogram-laboratory experiment)**

Reaction Parameters			
batch	water vol [mL][a]	NaOCl [equiv]	pH (reaction)
1	510	3.90	8.4

Responses					
run	yield	SP1	SP2	SP3	SM
1	74.3	0.00	0.00	0.00	0.00

[a] Normalized for 100-mmol scale reaction.

expected,[11] and minimal amounts of critical side products should be formed.

Verification of the Model. Experiments have been carried out using the predicted reaction conditions (Table 3).

The results obtained in experiments 1 and 2 confirm the reaction conditions predicted by the model. In none of the experiments was the level of side products detectable The lower yield in experiment 3 is due to loss of material during the filtration (manipulation problem).

Scale-Up in Kilogram Laboratory. The process was then scaled up to 1500 mmol, based on the starting material **1**, and one experiment was run in the kilogram-laboratory facility in a 20-L reactor. To make an easy comparison, values have been normalized to a laboratory-scale reaction (Table 4).

The results (Table 4) clearly demonstrate the reproducibility of the process when carried out in the optimal reaction conditions. The critical side products are formed at a level below the detection limit.

Table 5. **Reactions conditions and results (launch plant)**

Reaction Parameters			
batch[a]	water vol [mL][b]	NaOCl [equiv]	pH (reaction)
6, 7, 8	510	3.85	8.4

Responses					
batch	yield	SP1	SP2	SP3	SM
6	73.9	0.01	0.02	0.01	0.03
7	72.7	0.02	0.02	0.01	0.02
8	74.8	0.02	0.01	0.01	0.01

[a] Results are given for three batches at the middle of the production campaign. [b] Normalized for 100-mmol scale reaction.

Production in the Launch Plant. The production campaign was run in the launch plant using 2500-L reactors. The results of the experimental design were used to set up the reaction conditions relative to a batch size of 225 mol, based on starting material **1**. To make an easy comparison, values have been normalized to a laboratory-scale reaction (Table 5). Results are given for three batches produced in the middle of the production campaign (total 12 batches).

These results clearly demonstrate the reproducibility of the process when carried out in the optimal reaction conditions. All the critical side products are formed in just minimal amounts, well below the specified limit. Yields are slightly lower than expected, mainly due to some technical difficulties during the work-up (volume of solvent for the extraction/phase separation).

Conclusions

The use of an early phase RC-1, although not a traditional approach at the start of a project, is a powerful tool to get valuable information on a poorly characterized reaction. The information gained by such an experiment prompted us to rapidly consider scale-up issues, for instance the need to submit the starting material to a micronization. With such an analysis and a conservative setting of some factors it was possible to obtain a response surface model by combining the opposed responses in one single model. The results obtained in kilogram laboratory, as well as in the launch plant, represent a good confirmation of the validity of the model.

Acknowledgment

We thank our colleagues in the Chemical Research and Development department for their support and especially Dr. Colm O' Murchu for his valuable advice during the preparation of this manuscript.

Received for review May 24, 2004.

OP040014F

---

(11) For the ~20% missing yield, less than 5% can be attributed to loss of material. At least 15% represent the 10−12 different side products formed during the oxidation reaction. Most of these side products disappear during the workup. As mentioned, only three of them cause problems while, when formed, they remain in the final product. The goal of our work was to ascertain experimental conditions where their formation was minimized, allowing to get a conform material.