

Optimization by Response Surface Methodology (RSM) of the Kharasch–Sosnovsky Oxidation of Valencene

Ana Leticia García-Cabeza, Lindsey P. Ray, Rubén Marín-Barrios, María J. Ortega, F. Javier Moreno-Dorado, Francisco M. Guerra,* and Guillermo M. Massanet

Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Cádiz, 11510 Puerto Real, Cádiz, Spain

Supporting Information

ABSTRACT: Response surface methodology (RSM) has been employed to model and optimize the Kharasch–Sosnovsky allylic oxidation of valencene. The detailed effects of the amounts of oxidant, substrate, copper catalyst, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and temperature have been studied. The concentration of substrate and quantity of oxidant have been determined as the most significant variables. The interaction effects on the yield have been investigated using a three-level full-factorial design. The yield of benzoyloxyvalencene has been improved to 99%. Analysis of variance (ANOVA) has been used to evaluate the goodness of fit of the model.

INTRODUCTION

The search for new allylic oxidation reactions is a very active area in organic synthesis.¹ The presence of a double bond activates the allylic C–H bond, enabling the selective installation of an oxygenated function. The discovery of new ways to accomplish this transformation allows streamlining the synthesis of complex molecules, as White et al. have demonstrated in the preparation of highly complex compounds from the corresponding alkenes.² Recently, Hartwig et al. have demonstrated that the allylic oxidation of olefins is a useful method to extend the functionality along a carbon backbone by an iterative oxidation/homologation sequence.³

Classically, these oxidations have been performed by a series of metal-catalyzed processes, involving metals such as chromium, manganese, rhodium, iron, copper, cobalt, or palladium.⁴ It is noteworthy the wide use of those methods based on selenium reagents, which involve an ene reaction and a further [2,3] rearrangement. Selenium dioxide in catalytic or stoichiometric amounts has been a reagent of reference given its reliability and predictability.⁵ It produces, however, important amounts of organoselenium byproducts along with reduced forms of selenium, difficult to remove.

An alternative to the aforementioned methods is the Kharasch–Sosnovsky reaction, which involves the oxidation of an alkene by a peroxyester in the presence of a copper or cobalt source providing the corresponding allylic ester.⁶ The reaction was first described in the 1950s decade,⁷ and it remained unnoticed until the mid 1990s in which the Pfaltz,⁸ Katsuki,⁹ and Andrus¹⁰ groups developed enantioselective versions of the reaction.

Allylic oxidation is particularly attractive in terpene synthesis. These compounds exhibit remarkable biological activities, and their preparation is of high economic interest. Their synthesis is generally marked by the presence of multiple oxygenated functions in a relatively small carbon skeleton, which requires the employment of selective oxidation methods after the assembly of the carbon framework.¹¹

In the course of our research on the synthesis of thapsigargin, a family of sesquiterpene lactones with remarkable anti SERCA-ATPase activity,¹² the installation of an oxygenated function at an allylic position has been a recurring problem. Thapsigargin are characterized by the presence of a densely oxygenated carbon skeleton. Their synthesis is complex, and the synthetic intermediates were too valuable to be wasted in trials.¹³ We needed a model to test some of the reaction later assayed in the synthesis of thapsigargin. Valencene **1** seemed to meet our requirements: it is a commercially available sesquiterpene that presents two different double bonds, one exocyclic and another endocyclic. The different nature of these double bonds and the absence of other functional groups would simplify the analysis of the selectivity in the oxidation process.

In this work, we present our efforts to disclose the optimal conditions for the Kharasch–Sosnovsky allylic oxidation of valencene **1** (see Figure 1). In order to ensure the robustness of

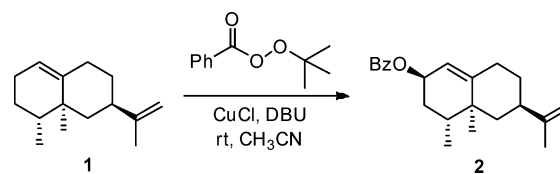


Figure 1. Kharasch–Sosnovsky oxidation of valencene.

the reaction, a design of experiments (DoE) approach has been employed.¹⁴ Although DoE has been widely adopted in fields such as analytical chemistry and chemical engineering, its use in organic synthesis in academia has not been very popular.¹⁵ Instead, the intuition of the researcher has been one of the main criteria in reaction optimization. Traditionally, an OVAT

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approach (one-variable-at-a-time) has been followed: a value for all of the variables that may affect the reaction outcome is set, and the effect on the response when only one variable is changed is studied. Nevertheless, an organic reaction is an excellent scenario for the application of DoE. The relative difficulty of the calculation methods and the need for the right choice of the experimental domain and the main variables have been the main drawbacks associated with this methodology. Nowadays, the use of modern statistic packages in conjunction with the current development of analytical techniques such as GC or LC makes possible a rapid optimization of a reaction with a smaller number of experiments.

RESULTS AND DISCUSSION

In a previous work, we have applied the simplex method to the optimization of the Kharasch–Sosnovsky oxidation of valencene **1**,¹⁶ obtaining the corresponding benzoate ester **2** in 55% yield.¹⁷ We came across this reaction after some initial attempts with SeO_2 and *tert*-butyl hydroperoxide (TBHP) as an oxidant system. We anticipated the regiochemistry of this reaction to be an issue since multiple positions were available for oxidation. Eventually, this transformation displayed poor selectivity, affording the primary and tertiary hydroxylated products resulting from the oxidation of the exocyclic double bond (at C-7 and C-13 positions), along with some overoxidation at C-13 leading to the corresponding aldehyde **5** (Figure 2).

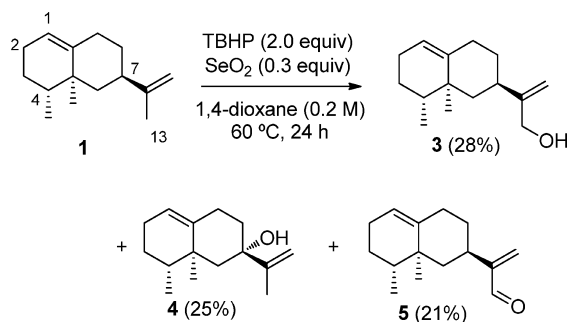


Figure 2. Allylic oxidation of valencene with SeO_2 and TBHP.

As expected, SeO_2 exclusively oxidized the exocyclic double bond. No insights of oxidation at C-2 was observed. Since we were more interested in the selective allylic oxidation of the endocyclic double bond, we decided to explore other possibilities as the above-mentioned Kharasch–Sosnovsky reaction for a complete optimization.

The simplex method employed in our initial study is based on a sequential optimization and can lead to good yields, but its efficiency strongly depends on the precise election of the initial conditions. Instead, the DoE approach studies the behavior of a system in an experimental domain, defined by a minimum and a maximum limit of the variables. Contrary to simplex, DoE reduces the experimental time since all experiments are run at the same time.

Response surface methodology (RSM)¹⁸ is one of the most relevant multivariate techniques in DoE. Prior to a study by RSM and to define the experiments to be carried out, it is necessary to choose the experimental domain. This is usually done by performing a previous screening design to determine which of the experimental variables and their interactions present more significant effects. Obviously, there are plentiful variables that may affect the response of a system, and it is virtually impossible

to identify and control all of them. It is therefore necessary to select carefully those variables that produce the major effects.

We decided to carry out a factorial 2^{5-1} screening design, considering the following variables (Table 1):

Table 1. Levels and variables for the Factorial 2^{5-1} design

variable	symbol	low level	high level	units
TBPP	x_1	1.00	2.50	equiv
CuCl	x_2	0.10	1.00	equiv
DBU	x_3	0.10	1.00	equiv
[valencene]	x_4	0.02	0.20	M
temperature	x_5	25	82	°C

(i) Equivalents of TBPP: at least one equivalent of TBPP is necessary to complete the reaction. A higher amount was thought to be beneficial, and the upper limit was set to 2.50 equiv;

(ii) Concentration of valencene: in order to ensure the adequate solubility, the range of valencene concentration was 0.02–0.20 M;

(iii) Equivalents of CuCl: a catalytic amount of CuCl was desired, but the role of the CuCl is not entirely clear in the mechanism. A stoichiometric amount was chosen for the upper limit;

(iv) Equivalents of DBU: again, the mechanistic role of DBU is unclear, although based on previous trials amounts smaller than 1 equiv seems to be sufficient for the reaction to proceed;

(v) Temperature: the lower and the upper levels are defined by the room temperature and the boiling point of the acetonitrile.

Previous trials showed that the reaction reached the highest yield at 20 h, and since no significant decreasing of the yield was observed, 24 h was selected as the reaction time for operational reasons (see Supporting Information).

This design allowed us to study the effect of five variables with 16 experiments and two replicates of the central point.¹⁹ The order of the experiments was randomized to diminish the effect of hidden variables. The experimental matrix and the yields are displayed in Table 2.

The graph of main effects shows the tendency line for each factor (Figure 3). Every line ranges from lower to higher levels.²⁰ From the above results, we concluded that the number of equivalents of TBPP, concentration of substrate, and temperature present a substantial impact on the response. However, the variation of the number of equivalents of CuCl and DBU did not influence appreciably on the yield. Considering that the temperature is limited by the boiling point of the solvent, it was decided to set the maximum value to 82 °C in further experiments. The effects of CuCl and DBU were slightly negative, which indicated that they should be kept at their lower levels (0.10 equiv of CuCl and 0.10 equiv of DBU).

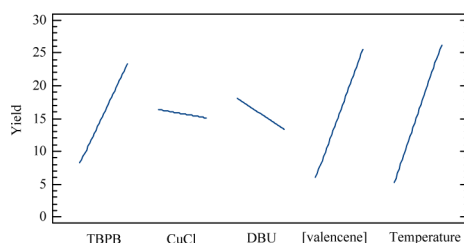
Taking into account these effects, we decided to set new conditions to obtain a response surface model. The range of the new experimental domain was redefined, increasing the equivalents of TBPP and the concentration substrate (Table 3).

In order to evaluate the curvature and to determine a maximum (the optimum yield), a second-order model was used. The selected design was a 3^2 design (three-level full-factorial design). This type of design is not convenient for more than two variables since a large number of experiments would be required. However, for two factors, it is affordable and presents a good efficiency.²¹ We assumed the yield to be affected by two independent variables (x_1 : TBPP equivalents; x_2 : valencene I

Table 2. Experimental matrix and results for Factorial 2^{5-1} design^a

run	variables					response
	x_1	x_2	x_3	x_4	x_5	yield ^b
1	1.00	1.00	0.10	0.20	82	11
2	1.00	1.00	1.00	0.20	25	9
3	1.00	0.10	1.00	0.02	25	0
4	2.50	0.10	1.00	0.02	25	0
5	2.50	1.00	1.00	0.02	25	0
6	1.00	0.10	0.10	0.20	25	3
7	2.50	0.10	1.00	0.20	25	5
8	2.50	0.10	0.10	0.02	25	0
9	1.75	0.55	0.55	0.11	54	32
10	2.50	1.00	0.10	0.20	25	3
11	1.00	0.10	0.10	0.02	82	7
12	1.00	1.00	0.10	0.02	25	0
13	1.00	1.00	1.00	0.02	82	0
14	1.00	0.10	1.00	0.20	82	14
15	2.50	0.10	0.10	0.20	82	80
16	1.75	0.55	0.55	0.11	54	30
17	2.50	1.00	1.00	0.20	82	57
18	2.50	1.00	0.10	0.02	82	19
19	1.75	0.55	0.55	0.11	54	29

^aAll reactions were carried out with valencene 1 (0.317 mL, 1.00 mmol), TBPB, CuCl, and DBU in amounts according to the table in refluxing acetonitrile for 24 h. ^bDetermined by GC.

**Figure 3. Main effects of the screening design.****Table 3. Levels and variables for the 3^2 design**

variable	symbol	low level	high level	units
TBPB	x_1	1.00	4.00	equiv
[valencene]	x_4	0.01	0.30	M

concentration), and the expected model would be represented by the following equation:

$$y = \beta_0 + \beta_1 x_1 + \beta_4 x_4 + \beta_{11} x_1^2 + \beta_{44} x_4^2 + \beta_{14} x_1 x_4 \quad (1)$$

where β_0 represents the independent term, β_1 and β_4 stand for the coefficients of the linear parameters, β_{11} and β_{44} are coefficients for the quadratic parameters, and β_{14} is the coefficient of the interaction parameters.

Table 4 shows the experimental matrix for the optimization of the conditions using this design, with nine experiments and three replicates of a central point.

To evaluate the goodness of the fitted model, the analysis of the variance (ANOVA) was accomplished. Therefore, an F -test to evaluate the significance of regression was made, comparing the ratio between the mean of squares of regression and the mean of squares of residuals with the Fisher distribution. When this ratio is higher than the tabulated F value (F_c), statistical significance can be concluded for the mathematical model, which

Table 4. Experimental matrix and results for 3^2 design^a

run	variables		response
	x_1	x_4	yield ^b
1	4.00	0.10	23
2	1.00	0.20	34
3	4.00	0.20	78
4	2.50	0.30	99
5	2.50	0.20	78
6	1.00	0.10	23
7	2.50	0.20	66
8	2.50	0.10	32
9	4.00	0.30	91
10	2.50	0.20	51
11	2.50	0.20	85
12	1.00	0.30	56

^aAll reactions were carried out with valencene 1 (0.317 mL, 1.00 mmol), TBPB, CuCl (10 mg, 0.10 mmol, 0.10 equiv), and DBU (0.015 mL, 0.10 mmol, 0.10 equiv) in refluxing acetonitrile for 24 h. ^bDetermined by GC.

Table 5. ANOVA results of the quadratic model for the yield of benzoyloxyvalencene 2^a

source	sum of squares	degree of freedom	mean squares	F values	critic F values (F_c)
model	7252.25	6	1192.11	5.89	4.95
residual	1011.60	5	202.32		
lack of fit	445.60	2	172.80	0.78	9.55
pure error	666.00	3	222.00		
total	8164.25	11			

^a $R^2 = 0.8761$; $R = 0.9360$; % adjustment = 93.60.

means that it is well-fitted to the experimental data. As shown in Table 5, a model F value of 5.89 for the yield of benzoyloxyvalencene 2 indicates that the model is significant. On the other hand, the lack of fit is not significant relative to pure error since its F value is 0.78, lower than F_c , which also accounts for the goodness of the model. The model explains the 88% of the variability in the yield of benzoyloxyvalencene 2, according to the obtained value for the R^2 coefficient (0.8761).

To identify the constants and coefficients for each variable, multiple regression analyses were performed by using the experimental data (Table 6).

Table 6. Regression coefficients and p values for benzoyloxyvalencene 2 yield

variables	coefficients	p values
constant	-46.0833	
x_1	32.3889	0.0476
x_4	370.8330	0.0018
x_1^2	-7.0556	0.0929
x_4^2	-587.5000	0.2264
$x_1 x_4$	58.3333	0.4879

Fitting the constants and coefficients, the equation that represents the chosen model is

$$y = -46.0833 + 32.3889x_1 + 370.8330x_4 - 7.0556x_1^2 - 587.5000x_4^2 + 58.3333x_1x_4 \quad (2)$$

Values of $p < 0.05$ indicate significant model terms. Both variables, TBPB ($p = 0.0476$) and concentration of valencene 1 ($p = 0.0018$) had a significant linear effect on the benzoyloxyvalencene 2 yield. Pareto plot shows these conclusions about the statistical significance of the effects. The vertical line in this graph indicates a level of 95% confidence. Horizontal bars that cross this line represent variables with greater influence on the yield of the reaction for that level of confidence (Figure 4).

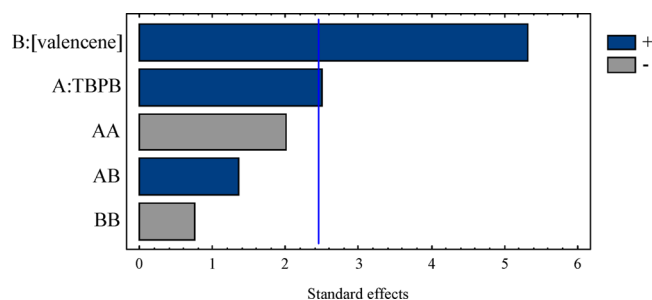


Figure 4. Pareto plot of 3^2 design for benzoyloxyvalencene 2.

An evaluation of the adequacy of the model was made by using the residuals from the least-squares fit. The normal probability plot of the residuals (Figure 5) indicates that normality assumptions are satisfactory since the residual plots cluster around the diagonal line.

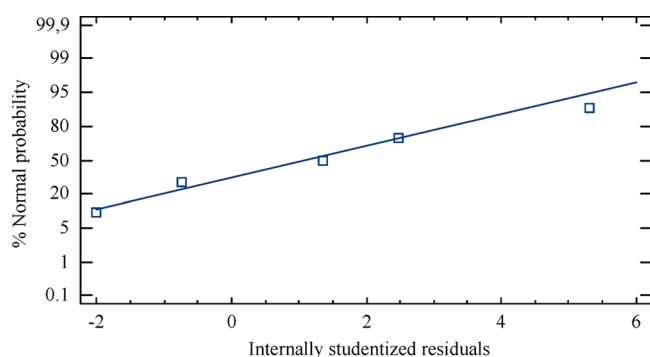


Figure 5. Normal probability of internally residuals.

Figure 6 represents the plot of residuals versus predicted responses. The residuals are distributed in a random fashion without any trend. These results imply that a maximum approximation on the relationship between variables and responses is provided by the obtained model.

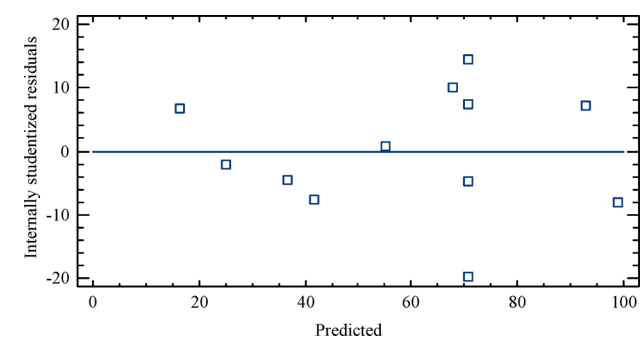


Figure 6. Plot of internally studentized residuals vs predicted for the yield of benzoyloxyvalencene 2.

It is possible to calculate the coordinates of the maximum (optimum yield) through the first derivative of the mathematical function. The visualization of the predicted model equation can be obtained by the surface response plot (Figure 7). The

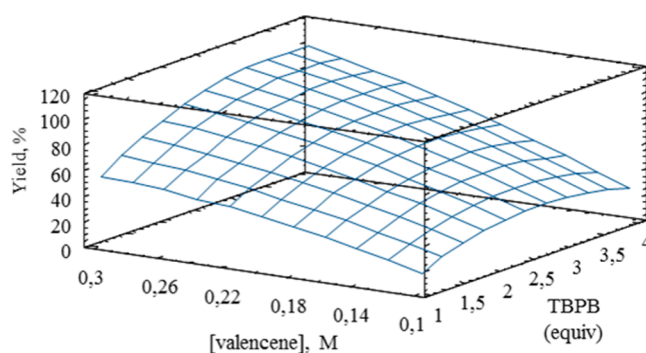


Figure 7. Response surface estimated for yield of benzoyloxyvalencene 2.

response surface as a function of the independent variables within the experimental range was generated by using the empirical model presented in eq 2. The plot indicates that the optimum yield was localized when we used 2.50 equiv of TBPB and a 0.30 M concentration of valencene 1.

After optimization by using the quadratic model, the predicted optimal conditions within the experimental domain were 3.54 equiv of TBPB and 0.30 M concentration. This set of conditions affords a predicted maximum yield of benzoyloxyvalencene 2 of 100.48%.

Finally, we decided to run an experiment with the predicted optimum conditions. This confirmation reaction led to 84% yield instead of the predicted 100%. However, a 99% yield was achieved experimentally with a lower amount of TBPB as shown in Table 7.

Table 7. Yields obtained for benzoyloxyvalencene 2 by the Kharasch–Sosnovsky reaction

conditions	TBPB (equiv)	[valencene] (M)	yield
experimental ^a	2.50	0.30	99 ^b
predicted	3.54	0.30	100
confirmed ^a	3.54	0.30	84 ^b

^aAll reactions were carried out with valencene 1 (0.317 mL, 1.00 mmol), TBPB, CuCl (10 mg, 0.10 mmol, 0.10 equiv), DBU (0.015 mL, 0.10 mmol, 0.10 equiv) in refluxing acetonitrile for 24 h. ^bDetermined by GC.

There is a discrepancy of 16% between the predicted and the confirmed experiments in Table 7. This result can be explained by considering that the Kharasch–Sosnovsky reaction takes place through a complex mechanism involving multiple species, including copper in different oxidation states and the formation of different radicals.^{6c} It is not surprising to find these discrepancies in such a complex organic reaction system. Anyhow, the increase in the yield of the reaction to 84% (found by the model optimization) and to 99% (found through the experimental design) has demonstrated the superior potential of the DoE approach compared to the classical OVAT methodology.²²

CONCLUSION

The optimization of the Kharasch–Sosnovsky allylic oxidation of valencene **1** has been accomplished. Different variables were selected for DoE and RSM designs and the reaction yield as the response was improved from 55 to 99%. According to the ANOVA analysis, the fitted model accounts for the behavior of the studied system. This is an example of the rapid and efficient optimization of a mechanistically unclear and complex chemical system and can serve as a guide for modeling organic reactions in academia.

ASSOCIATED CONTENT

Supporting Information

General considerations, optimized procedure for the Kharasch–Sosnovsky oxidation of valencene, and spectral data of 2-benzoyloxyvalencene. This material is available free of charge via the Internet at <http://pubs.acs.org>.

AUTHOR INFORMATION

Corresponding Author

*Tel.: +34-956012762. E-mail: francisco.guerra@uca.es.

Notes

The authors declare no competing financial interest.

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(19) It is possible to perform an initial screening design with a lower number of runs, but 16 reactions is an affordable number of experiments, and the obtained data would display less aliasing.

(20) Although the results presented some curvature, second-order effects could be confounded in the screening design. For this reason, curved graphics for the main effects are not displayed.

(21) In the case that a higher number of variables had been implied, other alternatives should have been considered. A central composite design would have been an appropriate choice.

(22) New refinements could lead to a more accurate model, but a 84% yield is good enough for synthetic purposes. In addition, the screening afforded conditions in which 99% yield was obtained. This means that although it cannot be concluded that the model is robust, the optimization process was successful.