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Perkin Reaction: Rapid and Efficient Process Optimization Through a Microwave/Design of Experiments Couple

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The Perkin Reaction: Rapid and Efficient Process Optimization Through a Microwave/Design of Experiments Couple

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Abstract.—Microwave chemistry and a Design of Experiments (DOE) protocol were employed together in order to rapidly and efficiently optimize a modified Perkin reaction. Microwave heating significantly reduced the reaction time, and the DOE provided a statistically significant understanding of underlying process relationships in a minimum number of experimental runs. In all, the reaction time was reduced from 1 hour to 2 minutes, factors important to yield were identified, an interesting cross-term interaction was discovered, and it was demonstrated that the more economical sodium acetate trihydrate catalyst was a viable alternative to the more costly anhydrous sodium acetate.

Key words:— Microwave chemistry, Design of Experiments (DOE) protocol, Perkin reaction, sodium acetate trihydrate catalyst, anhydrous sodium acetate.

Introduction

The base-catalyzed condensation of aromatic aldehydes with acid anhydrides, called the Perkin reaction, is a classical method for the synthesis of α,β-unsaturated carboxylic acids as shown in Equation 1 (March, 1985). A variation of this reaction involves the use of rhodanine instead of an acid anhydride as a route to a variety of biologically active compounds as shown in Equation 2 (Brown 1961, Foye and Torivich 1977). However, long reaction times and high temperatures (Mayo et al. 1994; Sykes, 1987) and/or exotic base catalysts (Vererkova et al. 1999) are required for the Perkin reaction.

(1)

(2)
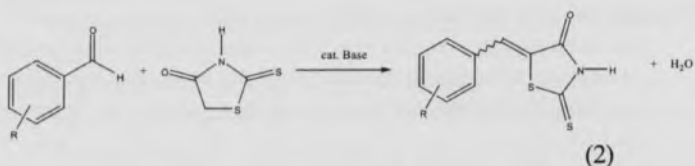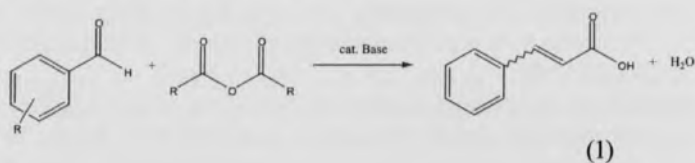
Acceleration of the reaction rate using microwaves could potentially reduce reaction times from hours to just a few minutes. Additionally, microwave heating is an efficient energy alternative over the classical thermal sources, which are highly inefficient.

Verekova, et al. (1999) reported that microwaves do accelerate the Perkin reaction (Equation 1), but their best yields were obtained after 10 minutes at 800-Watts using toxic cesium catalysts. Although sodium acetate is the most common base

catalyst, reports suggest that it must be anhydrous (Mayo et al. 1994). Given the previous long reaction time (10 minutes) at high microwave power (800 Watts) using a toxic catalyst (Vererkova et al. 1999), we decided to investigate optimizing this reaction using an efficient statistical approach called Design of Experiments (DOE). The acceleration of reactions using microwave chemistry combined with the resource efficiency of DOE constitutes a powerful process for optimizing chemical reactions. Herein, we demonstrate the utility of the microwave-DOE couple through the optimization of the Perkin reaction (Equation 2).

DOE is a large area of statistics that provides a way to consider the effects of all variables of a process on a set of outcomes. It does so in a uniform but simultaneous way through the construction of a mathematical model that has statistically significant predictive value within a defined design space (Box et al. 1978, Laird 2002). Chemists in the corporate sector have largely embraced DOE as a credible tool for optimizing processes, developing predictive models for reactions, and understanding complex variable interactions with a minimum of experiments (e.g., without having to run all possible combinations of variables and their levels) (Hendrix 1979, Owen et al. 2001). Historically, it appears that the academic sector has been reluctant (Lendrem et al. 2001) to employ DOE methods in chemical research, but this is beginning to change (Carlson et al. 2001, Carlson 2005). While DOE does not provide a comprehensive solution to process optimization, it does offer the chemist several advantages over the classical one-variable-at-a-time (OVAT) approach, including error analysis of the experimental process as well as the statistical model itself, detection of complex interactions between reaction parameters that influence experimental results, a finite number of experiments to reach research objectives, and the construction of a predictive mathematical model of the reaction within the experimenter-determined boundaries of the design (Bayne and

The Perkin Reaction: Rapid and Efficient Process Optimization Through a Microwave/Design of Experiments Couple

ubin, 1986). Common objections chemists have to the use of DOE for optimization of chemical processes include a lack of sufficient material resources or statistics trumping chemical intuition. Along with these, a host of other perceived obstacles have been adequately addressed in another forum (Lendrem et al. 2001).

Microwave assisted acceleration of organic reactions has emerged within the past twenty years as a viable alternative to conventional thermal methods (Hayes 2002, Marx 2004). Reactions carried out under conventional thermal conditions are often accompanied by long reaction times, undesired side product formation, and/or low yields. Microwave methodologies provide viable alternatives to classical thermal approaches for drug discovery efforts (Rose 2002), analytical chemistry (Kingston and Jassie 1988), protein synthesis (Yu et al. 1992), and green chemistry (Mingos 1994). Microwave techniques often provide the opportunity for carrying out organic transformations in a solventless or solid phase environment (Larhed et al. 2002).

Materials and Methods

Based on the fundamental chemical nature of this reaction, we believed that a 2-level designed experiment consisting of 4 factors (catalyst loading (**A**), acetic acid level (**B**), *o*-chlorobenzaldehyde level (**C**), and microwave time (**D**)) would provide the most information on underlying relationships affecting yield.   A 2-level screening experiment is the best option for revealing all main and two-factor (cross-term) effects. This 2-level, 4-factor DOE translated into 2^4 (16) experiments to uniformly cover the design space as shown in Table 1.

Inclusion of 6 center point experiments (all factors at midrange settings) provided a way to measure variability due to experimenter/process error. In other words, with a minimum of 6 center points, total error can be separated into two components: pure error due to the experiment and error due to model lack-of-fit. Table 1 shows the experiments carried out.

The experimental work was carried out in a domestic Panasonic® NN-S540 microwave oven equipped with an inverter that allowed for the actual lowering of the power output to a selectable level (e.g., 330 Watts; Varma and Namboodiri 2001). All chemicals were used as received without any further purification. A 5-mL conical vial was charged with 0.20 mmol rhodanine (Aldrich) and the appropriate amounts of sodium acetate trihydrate (Fisher) and glacial acetic acid (Fisher) as shown in Table 1. Using an automatic pipet, the appropriate volume of *o*-chlorobenzaldehyde (Aldrich) was added in one portion to the conical vial (Table 1). The vial was capped and placed in the microwave at 330 Watts for the appropriate time (Table 1). After microwaving, the vial was removed from the oven and placed in an ice-bath. The resulting yellow crystals were isolated via vacuum filtration and washed with 2 × 1-mL cold glacial acetic acid followed by 2 × 1-mL cold deionized water. Upon air drying, the yield was determined, and the

Table 1. Factor Settings for the 2-Level Experiment at 330-Watts Microwave Power

Run	Factor Settings			
	mmol NaOAc	mL HOAc	mmol o-CB	MW Time sec
1	0.500	0.500	0.200	30
2	0.500	0.500	0.200	120
3	0.0100	0.500	0.600	30.0
4	0.0100	0.500	0.200	30.0
5	0.500	0.500	0.600	30.0
6	0.0100	2.00	0.200	120
7	0.500	2.00	0.600	30.0
8	0.0100	0.500	0.600	120
9	0.255	1.25	0.400	75.0
10	0.255	1.25	0.400	75.0
11	0.500	2.00	0.200	30.0
12	0.0100	0.500	0.200	120
13	0.500	2.00	0.600	120
14	0.255	1.25	0.400	75.0
15	0.500	0.500	0.600	120
16	0.0100	2.00	0.600	120
17	0.0100	2.00	0.600	30.0
18	0.500	2.00	0.200	120
19	0.255	1.25	0.400	75.0
20	0.0100	2.00	0.200	30.0
21	0.255	1.25	0.400	75.0
22	0.255	1.25	0.400	75.0

melting point and infrared spectrum were obtained.

Results and Discussion

The singular reason why we chose microwave heating was to drastically shorten the reaction time. Clearly, without any statistical analysis, the efficacy of microwave heating was affirmed. However, the recommended 800 Watts of microwave heating (Verekova et al. 1999) was discovered to be somewhat excessive.   We found that 330 Watts of microwave heating provided the energy necessary for this reaction.

Another clear result from this set of experiments was the efficacy of the sodium acetate trihydrate catalyst. In general, anhydrous salts are difficult to prepare, hard to handle, and more costly than hydrates. Therefore, the fact that sodium acetate trihydrate proved to be a viable catalyst constitutes another significant improvement in this process.

The intent of the DOE was three-fold: 1) identify underlying relationships between factors, 2) develop a first-generation mathematical model of the process, and 3) provide insight for further development work. In the statistical analysis, the half-normal probability plot revealed that the main effects of all 4 factors as well as several cross-term interactions were significant
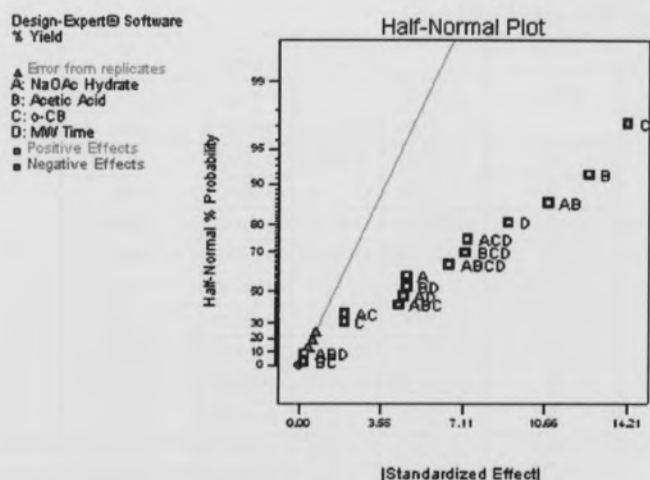
R. David Pace and Laura McWilliams

Fig. 1. Half-normal plot showing main and cross-term effects on the yield.

(Fig. 1). Half-normal probability plot is the fundamental method for selecting 2-level effects. In other words, the plot of the ordered values of a sample versus the expected ordered values from the true population will be approximately a straight line. Any terms that turn out to be important for the statistical model show up as outliers.

It should be pointed out that many 2-, 3-, and 4-factor terms appear to be significant, but such appearances can be deceiving. As shown in the ANOVA table (Table 2), effects that are significant in explaining process variability are clearly separated from effects that are not significant on the basis of the magnitude of the p-value. Small p-values (<0.05) suggest that there is model effect (e. g., the term is significant in explaining

process variability). This, however, is a screening experiment. Therefore, this experiment only gives us information concerning factors and interactions that may be important in explaining process variability of selected responses (i. e., yield) within the design space. What is clear is that the sodium acetate level, acetic acid volume, o-chlorobenzaldehyde level, and the microwave time significantly impacted yield as well as several interaction terms. The expression for the predicted yield is given as Equation 3.

$$Yield = 21.1 + 155.4A + 8.8B - 12.9C - 0.03D - 111.1AB - 362.7AC$$
$$- 1.43AD - 11.8BC - 0.05BD + 0.4CD + 206.9ABC$$
$$+ 0.8ABD + 4.1ACD - 0.03BCD - 2.0ABCD \qquad (3)$$

Interactions are best understood through 3-dimensional plots. Figure 2 shows three cube plots at the low, medium, and high microwave times (30 sec, 75 sec, and 120 sec), which reveal the behavior of the reaction yield at the extremes of the design space.

The lower right edges of the cube plots reveal a most interesting interaction (the CD interaction shown in Table 2) between o-chlorobenzaldehyde level (C) and microwave time (D). At 30 seconds microwave time, the best yield occurs with 0.50 mol NaOAc, 0.5 mL HOAc, and 0.20 mol (or, one equivalent) o-chlorobenzaldehyde. On the other hand, at 120 seconds microwave time, the best yield occurs with 0.50 mol NaOAc, 0.5 mL HOAc, and 0.60 mol (e. g., three equivalents) o-chlorobenzaldehyde. Figure 3 shows this CD cross-term interaction with two 3-D plots (one at 30 microwave seconds, the other at 120 microwave seconds) of the yield versus NaOAc level and o-chlorobenzaldehyde level. Clearly, after 30 seconds at 330 Watts, the optimum yield occured at the lowest level (1 equivalent) of o-chlorobenzaldehyde and the highest level of
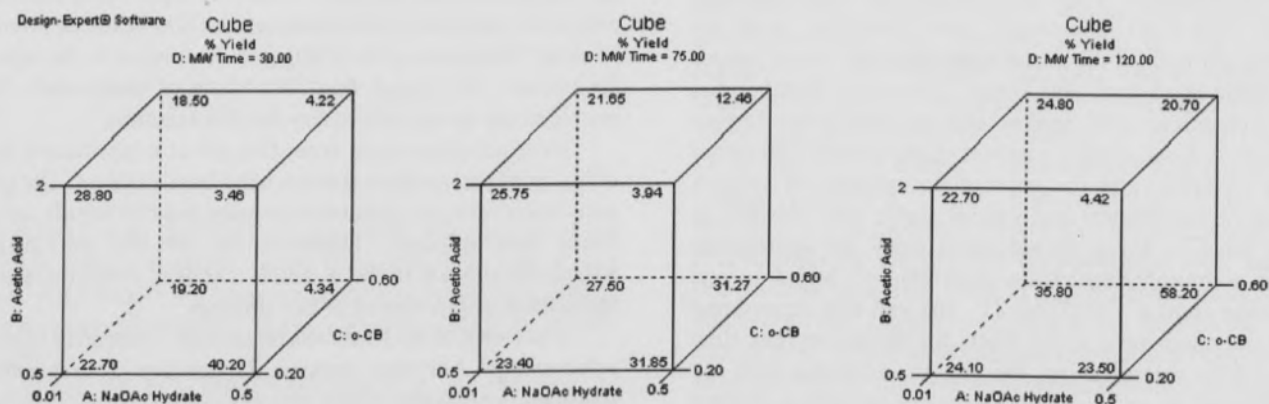

Fig. 2. Cube plots of the yield at the edges of the DOE design space.

The Perkin Reaction: Rapid and Efficient Process Optimization Through a Microwave/Design of Experiments Couple

Table 2. ANOVA Table for the DOE.

Source	Sum of Squares	Degrees of Freedom	Mean Square	F-Value	p-value Prob > F	Significant? Yes/No
Model	3195.584	15	213.0389	113.814	< 0.0001	Yes
A-NaOAc Hydrate	88.1721	1	88.1721	47.10509	0.0010	Yes
B-Acetic Acid	630.5121	1	630.5121	336.845	< 0.0001	Yes
C-o-CB	15.7609	1	15.7609	8.420109	0.0337	Yes
D-MW Time	331.24	1	331.24	176.9618	< 0.0001	Yes
AB	466.9921	1	466.9921	249.486	< 0.0001	Yes
AC	15.7609	1	15.7609	8.420109	0.0337	Yes
AD	82.81	1	82.81	44.24044	0.0012	Yes
BC	0.2025	1	0.2025	0.108184	0.7556	No
BD	87.9844	1	87.9844	47.00482	0.0010	Yes
CD	807.6964	1	807.6964	431.504	< 0.0001	Yes
ABC	74.8225	1	74.8225	39.9732	0.0015	Yes
ABD	0.2304	1	0.2304	0.123089	0.7400	No
ACD	213.7444	1	213.7444	114.1909	0.0001	Yes
BCD	209.0916	1	209.0916	111.7052	0.0001	Yes
ABCD	170.5636	1	170.5636	91.12196	0.0002	Yes
Curvature	1305.867	1	1305.867	697.6468	< 0.0001	Yes
Pure Error	9.359083	5	1.871817			
Cor Total	4510.81	21				

sodium acetate. Alternatively, after 120 seconds at 330 Watts, the optimum yield occured at the highest level (3 equivalents) of *o*-chlorobenzaldehyde and the lowest level of sodium acetate. The explanation for this unexpected result is not clear at this point. However, this *CD* interaction (or, any other interaction for that matter) would have gone undetected in the conventional OVAT method of experimentation.

At least three interactions (*AB, ABC,* and *ABCD*) identified in the DOE (see Table 2) may partially be explained by a combination of the facts that sodium acetate/acetic acid constitute a buffer system and that this modified Perkin reaction is acid catalyzed. Therefore, this suggests the possibility of a subsequent DOE where the levels of sodium acetate and acetic acid may be combined into one buffering pH term.

Conclusions

The DOE clearly identified that all 4 model factors are important in explaining the variability of the yield data. Further, an unexpected, but interesting, cross-term interaction was identified involving *o*-chlorobenzaldehyde and microwave time at 330 Watts (*CD*). Other interactions involving the coupling of sodium acetate and acetic acid suggest that combining these terms in a single buffering pH term may be important in subsequent work. Additionally, it was shown that the anhydrous sodium acetate catalyst could be replaced by the more economical trihydrate and that high wattage microwaves are not required for this process (330 Watts work as well as 800 Watts).

0.5 mL HOAc (Low Level)
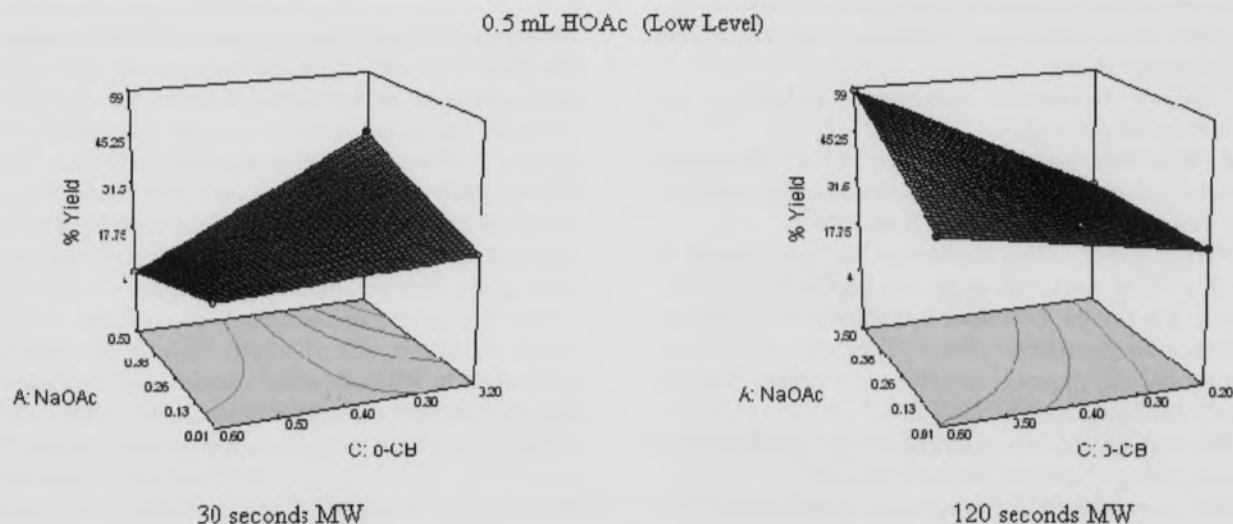

30 seconds MW

120 seconds MW

Fig. 3. 3-D plots of the yield within the design space.

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