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Short Communication

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Catalytic Benzylation of *o*-Cresol with Benzyl Alcohol: A Mathematical Model

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Abstract

Benzylation of *o*-cresol with benzyl alcohol (Bz-OH) in presence of 94% H_2SO_4 as catalyst was studied statistically with a two-levels three-factored experimental design to study the effects of single factor and effects of their interactions on the yield of benzylated product. Reaction temperature, molar ratio of *o*-cresol to Bz-OH and amount of 94% H_2SO_4 were considered as the major variables. A mathematical model was derived to calculate the predicted yield of benzyl *o*-cresol as $y = 0.419T+12.4055m+16.17w-0.0525Tm-2.606mw-0.094Tw+0.0175Tmw-6.25$; where, T = temperature (^oC), m = *o*-cresol to Bz-OH molar ratio, w = amount of catalyst (% by wt. of o-cresol) and y = yield. The adequacy of the suggested model was checked up and the discrepancies between the experimental and calculated values did not exceed ± 0.79%.

Key words : Benzylation, *o*-Cresol, Benzyl alcohol, Factorial design

Introduction

The benzylation of aromatic compounds is important in many sectors of the chemical industry. Benzylated phenols can be used as antioxidants in synthetic rubber, polypropylene, lubricating oil, wax, paper and lard (Ravikovich, 1964; Filbey *et al.,* 1985). Moreover some phenol derivatives are strong herbicides, bactericides and insecticides (Nemetkin *et al.,* 1951; Melinikov *et al.,* 1954). Benzylation of aromatic compounds using homogeneous acid catalysts is a commercially practiced Friedel-Craft type reaction (Olah, 1963) and Olah et al. are the pioneers of benzylation using various solid or protic acid catalysts (Olah *et al.,* 1966). Phenolic compounds have been benzylated/alkylated extensively with various reagents by several research groups (Abdurasulev and Israilova, 1962; Abdurasulev *et al.,* 1969; Ismailov, 1970; Olah *et al*., 1970; Olah *et al.,* 1972; Miller *et al*., 1982; Laali, 1985; Fukumoto *et al.,* 1996; Yadav and Badure, 2008). Synthetic, mechanistic, and kinetic aspects of benzylation have also been studied (Filbey *et al*., 1985; Wang and Ming, 1993). Reports are also available on the alkylation of isomeric cresols with alcohols in presence of different catalysts (Velu and Sivasankar, 1998; Grabowska and Wrzyszcz, 2001; Saha *et al.,* 2001; Zhang *et al.,* 2001; Krishnan *et al.*, 2002; Grabowska *et al.,* 2004; Yadav and Pathre, 2006), while benzylation of *o*-cresol with aromatic alcohols especially benzyl alcohol has not been studied so much. This classical reaction has been investigated statistically with the help of an experimental design.

The concept of experimental design is very much important to develop a new method, to improve an existing method or to avoid highly expensive experiments. Many books and reviews have been published on experimental design in chemometrics (Davies, 1979; Carlson, 1982; Atkinson and Donev, 1992; Deming and Morgan, 1993; Goupy, 1993; Grize, 1995). Experimental design is used to synthesize a product in an efficient way. The objectives are first to understand the effect of factors and their interactions and then to form a relationship between response and factors with a minimum number of experiments. Responses are dependent variables while factors are independent ones. In most cases, responses and factors are denoted by y and x ($x_1, x_2, \ldots x_s$), respectively and $y = f(x_1, x_2, \ldots x_s)$ where, s is the number of factors.

There are several profile analysis procedures available for estimating main effects of factors and their interaction effects (Box *et al*., 1978; Morgan, 1995). In this study, the 3-factors 2-levels Yates Pattern experimental design has been used for the analysis of benzylation of *o*- cresol with Bz-OH in presence of 94% H_2SO_4 (Clausen and Matson, 1978).

Materials and Methods

Chemicals used in this work were purchased from E. Merck (Germany) and were used as received. 94% H_2SO_4 was used as catalyst. Reagents were used without further purification, unless stated.

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The reactions were carried out in a three necked 250 mL round bottomed flask fitted with a condenser, a thermometer, a dropping funnel and a stirrer. *o*-Cresol-catalyst mixture was charged into the flask, heated to the temperature of the experiment, the Bz-OH was introduced into the mixture gradually over a certain period of time, 2 h (time of addition) with constant stirring. The reaction mixture was stirred for another period of time, 1 h (time of stirring) at the same temperature after the addition of the total amount of Bz-OH. The reaction mass was then cooled to room temperature and H_2SO_4 was neutralized with an equivalent amount of 10% KOH solution. The neutralized reaction mass was then dissolved in diethyl ether, washed with distilled water several times and dried with anhydrous magnesium sulfate keeping in a glass bottle. Unreacted reactants and solvent were distilled off at atmospheric pressure. The product thus obtained was subjected to fractionation by distillation and characterized by physico-chemical and spectral means (Rana *et al.,* 2003).

A statistical analysis of yields at various experimental parameters was performed to develop a mathematical model.

Results and Discussion

o-Cresol with Bz-OH in the presence of 94% H_2SO_4 as catalyst gave benzyl *o*-cresol (benzyl group attached to the aromatic ring at *o*- and *p*- positions with respect to the -OH group).

A series of experiments were designed for the preparative system. A design table helped in setting the factors in the experimental runs and calculation of the effects. In the preparation procedure, temperature, molar ratio of *o*-cresol to Bz-OH and amount of catalyst were considered as the three variables on which the yield depended significantly. Obviously, there were some other variables such as time of addition (t_a), time of stirring (t_s), stirring speed, etc. These variables were not included as factors in the experiment. The values of t_a, t_s and stirring speed were kept fixed at constant values of 2 h, 1 h and 300 rpm, respectively. The various values at which a factor was tested were called levels. The experimental levels of the variables used were as x_1 (temperature, ^oC) of 80 (low, -), 110 (medium, 0) and 140 (high, +); x_2 (molar ratio of *o*-cresol to Bz-OH) of 3:1 (low, -), 4:1 (medium, 0) and 5:1 (high, +); and x_3 (amount of catalyst, % by wt. of *o*-cresol) of 1 (low, -), 3 (medium, 0) and 5 (high, +). The yield of product was considered as the critical response of the experimental design.

The results of the experiments on benzylation are listed in Table I, for trials 1-8 defined by 2-level 3-factor designs as given in Table II and also for trial 9, the center point trial (x_1, x_2, x_3 were all kept at medium level, 0) was run four times. The variance was calculated and summarized in the last column of Table I.

Table I: Results of three-factor experiment

Trial	Yield			Range	Variance
	y_1	y_2	$\bar{y}$		
1	55.6	56.8	56.2	1	0.72
2	69.4	71.2	70.3	2	1.62
3	70.1	72.1	71.1	2	2.00
4	78.1	80.3	79.2	2	2.42
5	75.4	77.2	76.3	2	1.62
6	79.3	81.7	80.5	2	2.88
7	80.7	82.5	81.6	2	1.62
8	86.8	89.4	88.1	2	3.38
9	72.9 73.5	74.4 75.6	74.1	2	1.38

The average yield, y for each trial, the range and the variance were calculated for each trial.

The tabulated variances were then used in the calculation of pooled variance and it was estimated as 1.8545. Consequently, the pooled standard deviation (S_{pooled}) was calculated to be 1.362. The pooled standard deviation was used to calculate the minimum significant factor effect ([MIN]) and minimum significant curvature effect ([MINC]) a weighted average of the individual variances for each trial.

The difference between the average centre point value and the overall average of the design points indicated the severity of curvature. The computation analysis for this experiment is also shown in 6th to 9th columns of Table II. The design matrix was supplemented with a computation matrix, which was used to detect interaction effects. This computation matrix was generated by simple algebraic multiplication of the coded factor levels. The column at the far right of the table was the average yield for each trial. The sum +'s was calculated by the summation of the response values on each row with a plus sign for each column. In the similar manner the sum-'s was calculated. The sum of +'s and -'s should be equal for all factors and interactions and was used to check the calculations and design. The difference row represented the difference between the responses in the four trials when the factor was at a high level and that at a low level. The effect was then calculated by dividing the difference with the number of plus signs in the column. In the second column of Table II, (labeled as mean), the effect was the mean of all data points. The average of the centre point runs, Trial 9 (in Table I), was then subtracted from the mean effect to give a measure of curvature.

The [MIN] and [MINC] were derived from t-test significance criteria according to the following equations:

$$[MIN] = t.s\sqrt{\frac{2}{m.k}} \qquad \Lambda\,\Lambda\,\Lambda \quad (1)$$

$$[MINC] = t.s\sqrt{\frac{1}{m.k}+\frac{1}{c}} \qquad \Lambda\,\Lambda\,\Lambda \quad (2)$$

where t = appropriate value from "t table", s = pooled standard deviation, m = number of plus signs in column, k = number of replicates in each trial and c = number of center points.

The t value of 2.20 was taken from the Students' "t" table for the 95% confidence level and 11 degrees of freedom (Davies, 1979). The degree of freedom resulted from eight trials with two replicates and one trial with four replicates as: 8(2-1) + 1(4-1) = 11. Consequently, [MIN] and [MINC] are calculated as 1.4982 and 1.675 respectively.

By comparing the [MIN] and [MINC] values and effects calculated by experimental design (Table II) the significant factors and the interaction effects of the factors that influence the yields were determined. It was revealed that the effects of x_1, x_2, x_3 and the interactions between x_1 and x_3 (x_{13}), x_2 and x_3 (x_{23}) and x_1, x_2 and x_3 (x_{123}) were significant. There was no significant curvature effect. These results can be expressed as a mathematical model using a first order polynomial. The values for the co-efficients are one half of the factor effects listed in the Table II, since these are based on coded levels +1 and -1 that differed by two units. Therefore, the following mathematical model in which factors are in the coded form can be developed:

$$y = 75.41 + 4.1125x_1 + 4.5875x_2 + 6.2125x_3 - 1.4375x_1x_3 - 1.3625x_2x_3 + 1.04x_1x_2x_3 \qquad \Lambda\,\Lambda\,\Lambda \quad (3)$$

The coded units in Eq. (3) can be converted into real units by substituting their values.

For temperature, $$x_1 = \frac{T - \frac{(140+80)}{2}}{\frac{(140-80)}{2}} = \frac{T-110}{30}$$

For molar ratio, $$x_2 = \frac{m - \frac{(5+3)}{2}}{\frac{(5-3)}{2}} = m-4$$

For amount of catalyst, $$x_3 = \frac{w - \frac{(5+1)}{2}}{\frac{(5-1)}{2}} = \frac{w-3}{2}$$

Table II: Computational matrix for three-factor experiments

Trial	Mean	Design			Computation				Respones
		x_1	x_2	x_3	x_{12}	x_{13}	x_{23}	x_{123}	$\bar{y}$
1	+	-	-	-	+	+	+	-	56.2
2	+	+	-	-	-	-	+	+	70.3
3	+	-	+	-	-	+	-	+	71.1
4	+	+	+	-	+	-	-	-	79.2
5	+	-	-	+	+	-	-	+	76.3
6	+	+	-	+	-	+	-	-	80.5
7	+	-	+	+	-	-	+	-	81.6
8	+	+	+	+	+	+	+	+	88.1
Sum +'s	603.3	318.1	320	326.5	299.8	295.9	296.2	305.8	
Sum -'s	0	285.2	283.3	276.8	303.5	307.4	307.1	297.5	
Sum	603.3	603.3	603.3	603.3	603.3	603.3	603.3	603.3	
Difference	603.3	32.9	36.7	49.7	-3.7	-11.5	-10.9	8.3	
Effect	75.41	8.225*	9.175*	12.425*	-0.925	-2.875	-2.725*	2.08*	

Curvature = 75.41 - 74.1 = 1.31

where, T = temperature (^oC); m = molar ratio of *o*-cresol to Bz-OH and w = amount of H_2SO_4, % by wt. of *o*-cresol.

The substitutions of x_1, x_2, x_3, x_{13},, x_{23}, and x_{123} values in Eq. (3) yield the final mathematical model:

$$y = 0.419T + 12.4055m + 16.17w - 0.0525Tm - 2.606mw - 0.094Tw + 0.0175Tmw - 6.52 \quad ..(4)$$

The experimental yield and calculated yield showed a good agreement (Table III). Thus the application of statistical design is able to provide a convenient set of experimental conditions for the synthesis of benzyl *o*-cresol.

Table III: Comparison of experimental and predicted yields.

Trial	Experimental yield (%)	Predicted yield (%)	Percentage deviation
1	56.2	56.65	0.79
2	70.3	69.85	0.64
3	71.1	70.65	0.64
4	79.2	79.65	0.56
5	76.3	76.78	0.63
6	80.5	80.02	0.60
7	81.6	81.13	0.58
8	88.1	88.57	0.53

Experimental conditions: Time of addition: 2 h; time of stirring: 1 h.

Conclusion

The yield of benzylation of *o*-cresol with Bz-OH in presence of 94% sulfuric acid was optimized by means of experimental design. Results of this study indicated that all the three variables, e.g., temperature, molar ratio of *o*-cresol to Bz-OH and amount of sulfuric acid, and interactions between temperature and amount of sulfuric acid (x_{13}), molar ratio of *o*-cresol to Bz-OH and amount of sulfuric acid (x_{23}) and temperature, molar ratio of *o*-cresol to Bz-OH and amount of sulfuric acid (x_{123}) significantly affect the yield. The calculated (predicted) yield showed a good agreement with the experimental yield and the discrepancies were within ±0.79%. Thus the derived mathematical model can provide a convenient set of experimental conditions for the process under consideration.

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