

# Central composite experimental design applied to the catalytic carbon-sulfur bond formation by fluorapatite catalyst

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**Abstract:** The aim of this study was to apply experimental design in the optimization of the thia-Michael addition reaction between chalcone derivatives and mercaptans catalyzed by Fluorapatite catalyst (FAP). The central composite design was used to design an experimental program to provide data to model the effects of various factors on reaction yield ( $Y$ ). The variables chosen were catalyst weight ( $X_1$ ), reaction time ( $X_2$ ) and solvent volume ( $X_3$ ). The mathematical relationship of reaction yield on the three significant independent variables can be approximated by a nonlinear polynomial model. Predicted values were found to be in good agreement with experimental values. The optimum reaction conditions ( $x_1= 350$  mg,  $x_2= 30$  min and  $x_3= 2$  mL) for reaction model (chalcone and thiophenol) obtained by response surface were applied to other substrates. This study has shown that central composite design could efficiently be applied for the modeling of catalytic carbon-sulfur bond formation by FAP catalyst under mild reaction condition with high yield, and it is an economical way of obtaining the maximum amount of information with the fewest number of experiments.

**Keywords:** Carbon-Sulfur Bond Formation, Fluorapatite, Heterogenous Catalyst, Central Composite Design, Response Surface Methodology

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## 1. Introduction

Thia-Michael addition reaction is a very useful method for carbon-sulfur bond-forming in organic synthesis [1]. This reaction also plays critical roles in the biosynthesis [2] and synthesis of bioactive compounds [3] and provides a means to protect the olefinic double bond of  $\alpha,\beta$ -unsaturated carbonyl groups [4]. The resultant 2-sulfido carbonyl compounds undergo copper (I)-induced or oxidative thermolytic elimination of the sulfur moiety for easy regeneration of the  $\alpha,\beta$ -unsaturated carbonyl groups [5]. The  $\beta$ -sulfido carbonyl compounds serve as starting materials for  $\beta$ -acylvinyl cation [6] and homoenolate [7] equivalents. Thus, there have been significant efforts towards the development of methodologies for thia-Michael addition [8].

Traditionally, the 1,4-addition of mercaptans to  $\alpha,\beta$ -unsaturated carbonyl compounds is catalyzed by strong

bases such as alkali metal alkoxides [9], hydroxides [10], and amines [11]. However the use of either strongly acidic or basic conditions [12] frequently leads to the formation of undesirable side products owing to competing reactions, such as polymerization, self-condensation and rearrangements.

Nevertheless, advantages of the heterogeneous synthesis are very interesting; reactions take place in simple and mild conditions [13]. The products obtained are generally pure and separated easily. Thus, numerous organic reactions have been carried out in solid/liquid heterogeneous media. So, several types of catalysts or solid supports have been studied, we can mention hydrotalcite [14], alumina [15], montmorillonite [16], zeolites [17], natural phosphate [18], animal bone meal [19] and hydroxyapatite [20].

In continuation of our ongoing program to develop a heterogeneous catalysis, we describe in this paper, the investigation of central composite design for modeling and optimization of the thia-Michael addition reaction between

chalcone derivatives and mercaptans catalyzed by Fluorapatite catalyst under mild reaction condition.

## 2. Materials and Methods

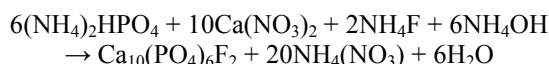
### 2.1. Chemicals and Instrumentations

All commercial reagents and solvents were used without further purification. X-ray diffraction (XRD) patterns of the catalysts were obtained on a Philips 1710 diffractometer using Cu-K $\alpha$  radiation. Surface areas were determined at 77 K using a Coulter SA 31000 instrument with an automated gas volumetric method employing nitrogen as the adsorbate. NMR spectra were recorded on a Bruker ARX 300 spectrometer. Mass spectra were recorded on a VG Autospec spectrometer. FTIR spectra were recorded on an ATI Mattson-Genesis Series spectrophotometer using the KBr disc method.

### 2.2. Preparation and Characterization of Catalyst

#### 2.2.1. Preparation of the Fluorapatite

The preparation of the Fluorapatite catalyst (FAP) was carried out by the co-precipitation method [21] using diammonium phosphate, calcium nitrate and ammonium fluoride in presence of ammonia by the following reaction:



250 mL of a solution containing 7.92 g of diammonium hydrogen phosphate and 1 g of ammonium fluoride, maintained at pH greater than 12 by addition of ammonium hydroxide (15–20 mL), were dropped under constant stirring into 150 mL of a solution containing 23.6 g calcium nitrate ( $\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$ ). The suspension was refluxed for 4 h. Doubly distilled water (DDW) was used to prepare the solutions.

The FAP crystallites were filtered, washed with DDW, dried overnight at 80°C and calcined in air at 700°C for 30 min before use.

#### 2.2.2. Characterization of the Fluorapatite

The structure of final product FAP was confirmed by X-ray diffraction and infrared spectra. The lattice parameter of this apatite is in excellent agreement with standard data:  $a=9.364$  and  $9.422$  Å and  $c=6.893$  and  $6.883$  Å.

Surface area for calcined FAP was determined by the BET method from the adsorption–desorption isotherm of nitrogen at its liquid temperature (77 K) and was found to be  $S=15$  m<sup>2</sup> g<sup>-1</sup>. The total pore volume was calculated by the BJH method at  $P/P_0=0.98$  ( $V_t=0.0576$  cm<sup>3</sup>/g).

### 2.3. General Procedure

The general procedure is reported in Figure 1, as follows: To a flask containing an equimolar mixture (1 mmol) of Michael donors 2 and Michael acceptors 1 in methanol catalyzed by FAP was added and the mixture was stirred at

room temperature until completion of the reaction, as monitored by thin layer chromatography.

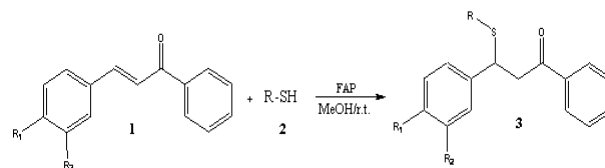


Figure 1. Thia-Michael addition reaction catalyzed by Fluorapatite

The catalyst was filtered, washed with dichloromethane and the filtrate was concentrated under reduced pressure. The crude product was purified by recrystallization. The product was analyzed by <sup>1</sup>H, <sup>13</sup>C NMR and IR spectrometry.

### 2.4. Statistical Analysis

A central composite rotatable design [22] for  $k$  independent variables was employed to design the experiments in which the variance of the predicted response,  $\hat{Y}$ , at some points of independent variables,  $X$ , is only a function of the distance from the point to the design centre. The design of experiment is intended to reduce the number of experiments and to arrange the experiments with various combinations of independent variables. In the rotatable design, the standard error, which depends on the coordinates of the point on the response surface at which  $\hat{Y}$  is evaluated and on the coefficients  $\beta$ , is the same for all points that are the same distance from the central point.

These designs consist of a  $2^k$  factorial (coded to the usual  $\pm 1$  notation) augmented by  $2 \cdot k$  axial points ( $\pm\alpha, 0, 0$ ), ( $0, \pm\alpha, 0$ ), ( $0, 0, \pm\alpha$ ), and 2 centre points ( $0, 0, 0$ ). The value of  $\alpha$  for rotatability depends on the number of points in the factorial portion of the design, which is given in Eq. (1) :

$$\alpha = (N_F)^{1/4} \quad (1)$$

Where  $N_F$  is the number of points in the cube portion of the design ( $N_F = 2^k$ ,  $k$  is the number of factors). Since there are three factors, the  $N_F$  number is equal to  $2^3 (=8)$  points, while  $\alpha$  is equal to  $(8)^{1/4} (=1.682)$  according to Eq. (1).

In this study, the response was reaction yield ( $Y_{R\%}$ ). Each response was used to develop an empirical model that correlated the response to the reaction conditions variables for catalytic carbon-sulfur bond formation, using a second-degree polynomial equation as given by Eq. (2):

$$\hat{Y} = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_{12} X_1 X_2 + \beta_{13} X_1 X_3 \\ + \beta_{23} X_2 X_3 + \beta_{11} X_{12} + \beta_{22} X_{22} + \beta_{33} X_{32} \quad (2)$$

Where  $\beta_0$  the constant coefficient,  $\beta_i$  the linear coefficients,  $\beta_{ij}$  the cross-product coefficients and  $\beta_{ii}$  is the quadratic coefficients.

The software STATGRAPHICS-Plus was used for the experimental design, data analysis, model building, and graph plotting.

### 3. Results and Discussion

#### 3.1. Reaction Model

Conjugate addition between chalcone (X=H) and thiophenol (R=Ph) were chosen as model substrates to determine suitable reaction conditions for the catalytic carbon-sulfur bond formation by FAP catalyst.

#### 3.2. Experimental Design

Preliminary experiments were carried out to screen the appropriate parameters and to determine the experimental domain. From these experiments, the effects of catalyst weight ( $X_1$ ), reaction time ( $X_2$ ) and solvent volume ( $X_3$ ) are investigated on reaction yield as response. The parameter levels and coded values were given in Table 1.

Table 1. Study field and coded factors

Natural variable	Unit	Coded variables $X_1, X_2$ and $X_3$		
		-1	0	+1
$x_1$ =Catalyst weight	mg	200	400	600
$x_2$ =Reaction time	min	15	25	35
$x_3$ =Solvent volume	mL	1.5	3	4.5

The experimental design matrix and the corresponding experimental parameters and response value were shown in Table 2.

Table 2. Experimental design and results

Order	Coded units of variable			Reaction yield
	$X_1$	$X_2$	$X_3$	
01	+1	+1	+1	93
02	+1	+1	-1	80
03	+1	-1	+1	67
04	+1	-1	-1	62
05	-1	+1	+1	82
06	-1	+1	-1	94
07	-1	-1	+1	39
08	-1	-1	-1	63
09	-1.682	0	0	72
10	+1.682	0	0	81
11	0	-1.682	0	46
12	0	+1.682	0	96
13	0	0	-1.682	78
14	0	0	+1.682	72
15	0	0	0	94
16	0	0	0	96

The final empirical model in term of coded factors after excluding the insignificant terms for reaction yield ( $\hat{Y}_{R\%}$ ) is shown in Eq. (3) :

$$\hat{Y}_{R\%}=95,0389+2,86568*X_1+14,7977*X_2-2,0569*X_3-6,6346*X_1^2-8,57915*X_2^2-7,16493*X_3^2-3,75*X_1X_2+6,75*X_1X_3+2,5*X_2X_3 \quad (3)$$

Positive sign in front of the terms indicates synergistic effect, whereas negative sign indicates antagonistic effect. The quality of the model developed was evaluated based on the correlation coefficient value.

The  $R$  value for Eq. (3) was 0.9993. The  $R$  value obtained was relatively high, indicating that there was a good agreement between the experimental and the predicted values from the model.

The  $R^2$  value for Eq. (3) was 0.9986. This indicated that 99.86% of the total variation in the reaction yield was attributed to the experimental variables studied. From the statistical results obtained, it was shown that the above model was adequate to predict the reaction yield within the range of variables studied.

The adequacy of the model was further justified through analysis of variance (ANOVA).

The ANOVA for model for reaction yield is listed in Table 3. From this ANOVA, the Model  $F$ -value of 540 implied that the model was significant. Values of  $Prob. > F$  less than 0.01 indicated that the model terms was significant. In this case, the linear terms ( $X_1, X_2$  and  $X_3$ ), the squared terms ( $X_1^2, X_2^2$  and  $X_3^2$ ) and the interaction terms ( $X_1X_2, X_1X_3$  and  $X_2X_3$ ) were significant model terms. It appears that all effects are significant.

Interactions between independent variables are shown in three-dimensional surface plots with other variable being at fixed level (Fig. 2 A-D).

Figure 2-A and 2-B shows the interaction between catalyst weight ( $X_1$ ) and reaction time ( $X_2$ ) at constant value of the solvent volume ( $X_3=+1$ ) and ( $X_3=-1$ ).

Interaction between catalyst weight ( $X_1$ ) and solvent volume ( $X_3$ ) at constant value of the reaction time ( $X_2=0$ ) is shown in Figure 2-C.

Figure 2-D shows the interaction between reaction time ( $X_2$ ) and solvent volume ( $X_3$ ) at constant value of the catalyst weight ( $X_1=0$ ).

#### 3.3. Optimizing Reaction Conditions

The main objective of this research is to determine the best reaction conditions to conjugate addition between chalcone and thiophenol.

Then, using above-mentioned methodology for experimental design, the ranges of the parameters required to obtain optimum conditions were determined. In this optimization study, reaction yield was chosen as the objective function. Furthermore, optimum conditions are often calculated in the presence of some constraints which ensure them to be more realistic. If the model used in the optimization study is an empirical one, high and low levels

of the process parameters in the experimental design are considered, inevitably, as explicit constraints, in order to avoid extrapolation. Thus, the optimization problem for response is defined as:

Maximize:

$$\hat{Y}_{R\%} = \text{Max } \hat{Y}_{R\%} \quad (4)$$

Constraints on the parameters  $X$ :

$$-a_i < X_i < +a_i \quad i=1,2,3 \quad (5)$$

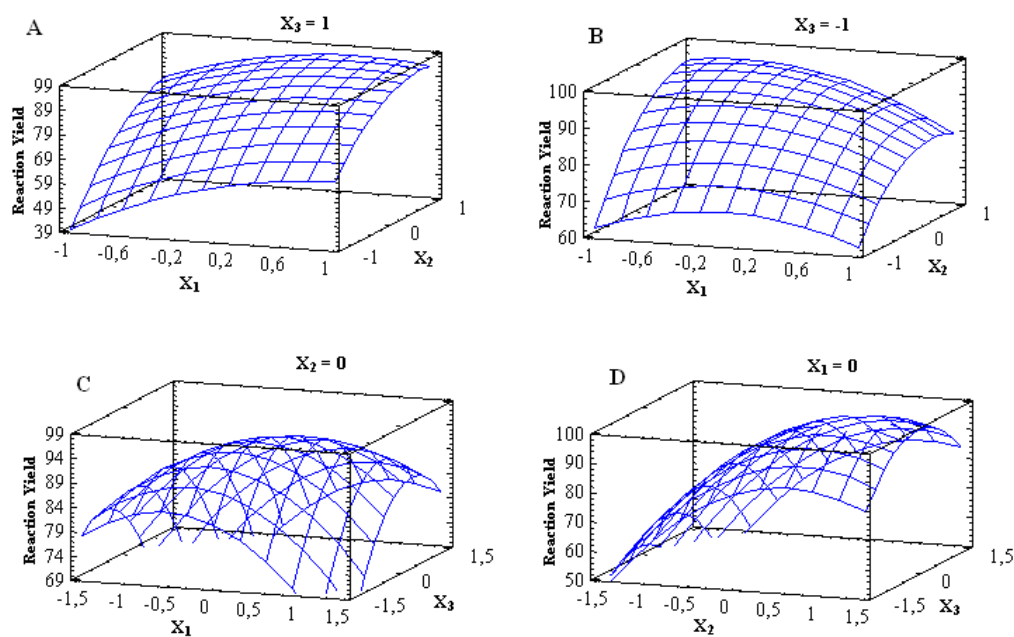
The investigation of equation 3 showed that, if  $X_1 = 0.25$ ,  $X_2 = 0.50$  and  $X_3 = -0.67$ ; the value predict from the results using response surface model is 98%. The experimental checking in this point, i.e. under the optimum reaction conditions such as: catalyst weight = 350 mg, reaction time = 30 min and solvent volume = 2 mL with high reaction yield 96%, confirms this result.

**Table 3.** Regression variance analysis for the model

Source of variation	Coefficient	Sum of Squares	v	Mean square	F <sub>exp</sub>	Significance test
Regression	-	4559.3112	9	506.59013	539.998974	*
$\beta_0$	95.0389	-	1	-	-	
$\beta_1$	02.8657	0112.1520	1	0112.1520	0119.55	**
$\beta_2$	14.7977	2990.4600	1	2990.4600	3187.67	**
$\beta_3$	-02.0569	0057.7798	1	0057.7798	0061.59	**
$\beta_{11}$	-06.6346	0407.7860	1	0407.7860	0434.68	**
$\beta_{12}$	-03.7500	0112.5000	1	0112.5000	0119.92	**
$\beta_{13}$	06.7500	0364.5000	1	0364.5000	0388.54	**
$\beta_{22}$	-08.5792	0681.8850	1	0681.8850	0726.82	**
$\beta_{23}$	02.5000	0050.0000	1	0050.0000	0053.30	**
$\beta_{33}$	-07.1649	0475.5840	1	0475.5840	0506.95	**
Residue	-	0005.62879	6	0.9381316	-	
Total	-	4564.94000	15	-	-	

\* Significant at a level of 1%  $F_{0.01}(9, 6) = 7,98$

\*\* Significant at a level of 1%  $F_{0.01}(1, 6) = 13,75$



**Figure 2.** Response surface graphs for interactions between independent variables with other variable being at fixed level

### 3.4. Catalytic Carbon-Sulfur Bond Formation

To determine the scope and limitation of this reaction, the optimum condensations were applied to other substrates as shown in table 34.

Several structurally varying donors(2) such as thiophenol, 2-aminothiophenol and ethyl thioglycolate underwent clean and remarkably FAP catalyst thia-Michael addition with a variety of acceptors(1) including simple and substituted chalcones.

The products of undesirable side reactions resulting from 1,2 addition, polymerization and bis-addition are not observed. The yields obtained with synthetic phosphate FAP are very high and exceed 81 %, except for the products (3l, 3m and 3o). In this case, the low reactivity observed may be due to low nucleophilicity of ethyl thioglycolate or to the

presence an electron-donor, the same similar effect has been observed with others solid state phosphates in heterogeneous catalysis.

The use of FAP catalyst is particularly interesting since it's regenerated by calcinations at 700°C during 15 min, and after five successive recoveries, product 3a was obtained with same yield. Thus, we estimate that the surface of the synthetic phosphate presents certainly multicatalytic active sites.

The basic sites (CaF<sub>2</sub> and oxygen of PO<sub>4</sub> group) enhance the thiol nucleophilicity.

The acidic sites (Ca<sup>+</sup> and phosphorus PO<sub>4</sub> group) probably increase the enone moiety polarization.

Consequently, the carbon-sulfur bond formation is accelerated and the sulfanyl product is obtained by the transfer of proton.

Table 4. Synthesis of sulfanyl derivatives catalyzed by Fluorapatite

Products	R <sub>1</sub>	R <sub>2</sub>	R	Yield %
3a	H	H	-Ph	96
3b	H	H	-2-NH <sub>2</sub> -Ph	94
3c	H	H	-CH <sub>2</sub> -CO <sub>2</sub> -Et	76
3d	H	<i>m</i> -NO <sub>2</sub>	-Ph	94
3e	H	<i>m</i> -NO <sub>2</sub>	-2-NH <sub>2</sub> -Ph	96
3f	H	<i>m</i> -NO <sub>2</sub>	-CH <sub>2</sub> -CO <sub>2</sub> -Et	87
3g	<i>p</i> -Cl	H	-Ph	95
3h	<i>p</i> -Cl	H	-2-NH <sub>2</sub> -Ph	92
3i	<i>p</i> -Cl	H	-CH <sub>2</sub> -CO <sub>2</sub> -Et	81
3j	<i>p</i> -Me	H	-Ph	83
3k	<i>p</i> -Me	H	-2-NH <sub>2</sub> -Ph	95
3l	<i>p</i> -Me	H	-CH <sub>2</sub> -CO <sub>2</sub> -Et	54
3m	<i>p</i> -OMe	H	-Ph	72
3n	<i>p</i> -OMe	H	-2-NH <sub>2</sub> -Ph	94
3o	<i>p</i> -OMe	H	-CH <sub>2</sub> -CO <sub>2</sub> -Et	48

## 4. Conclusion

The use of a central composite design for the optimization of catalytic carbon-sulfur bond formation using Fluorapatite as a catalyst was found to be effective in the study of the influence of different variables on this thia-Michael addition reaction. The three variables catalyst weight, reaction time and solvent volume significantly influenced the reaction yield. The regression model adequately explained the variation in the data and significantly represented, at a 95% confidence limit, the relationship between the independent variables and the response.

The FAP catalyst showed good performance with a high yield and the separation of the catalyst is easy by simple filtration.

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