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Experimental design and modeling of heterogeneous catalytic activity for synthetic phosphate in conjugate addition

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Abstract

The heterogeneous catalytic activity of synthetic phosphate for conjugate addition was studied. This catalyst was prepared by calcination a mixture of fluorapatite and sodium nitrate. The conjugate addition between p-methoxychalcone and thiophenol has been used as model reaction. A central composite design was successfully employed for experimental design and analysis of the results. The combined effect of reaction time (X1), solvent volume (X2), catalyst weight (X3) and impregnation ratio (X4) on the reaction yield (Y) was studied and optimized using response surface methodology.

1. Introduction

The use of solid basic and acidic catalysts has attracted attention in different areas of organic synthesis because of their advantages like environmental compatibility, reusability, high selectivity and convenient use and separation of products.

Indeed, the use of heterogeneous catalysts [1] allows a simplification of the purification step to a simple filtration, separating the catalyst from the reaction media.

In recent years, the organic reaction in heterogeneous media has been carried out in presence of several types of catalysts or solid supports, we can mention hydrotalcite [2], alumina [3], montmorillonite [4], zeolites [5], natural phosphate [6], animal bone meal [7], hydroxyapatite [8], synthetic diphosphate $Na_2CaP_2O_7$ [9], silica [10] and other catalysts with more or less success.

The Fluorapatite [11] catalyst is easily prepared from cheaper starting materials and is insoluble in organic solvents as well as water and very stable even at high temperatures, which makes catalyst recycling very convenient. However, little attention has been given to the usage of Fluorapatite as a catalyst in organic reactions. In the last years, it was utilized as an efficient heterogeneous solid catalyst for organic synthesis in a few cases.

The Fluorapatite catalyst was successfully used for catalyzing several reactions such as Knoevenagel reaction [12], Michael addition [13], Synthesis of α,β-unsaturated arylsulfones [14], Hydration of nitriles [15], Friedel–Crafts alkylation [16], Transesterifications [17] and Biginelli reaction [18].

In continuation of our research work to develop a heterogeneous catalysis, we studied in this paper, the heterogeneous catalytic activity of synthetic phosphate in the organic reaction using response surface methodology [19].

The synthetic phosphate was prepared by calcination a mixture of fluorapatite and sodium nitrate. The conjugate addition between *p*-methoxychalcone and thiophenol has been used as model reaction.

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-Kα 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 the Fluorapatite

The preparation of Fluorapatite catalyst (FAP) is carried out by co-precipitation method using diammonium phosphate, calcium nitrate and ammonium fluoride in presence of ammonia. The FAP obtained was calcined at 900 °C before use.

The structure of this catalyst was confirmed by X-ray diffraction, infrared spectra and chemical analysis.

The surface area for calcined FAP catalyst was determined by the BET method and found to be S=15.4 $m^2\ g^{-1}$.

The total pore volume was calculated by the BJH method at P/P_0=0.98 and found to be V_T=0.0576 $cm^3\ g^{-1}$.

2.3. Preparation and Characterization of the modified Fluorapatite

The modified Fluorapatite catalyst (Na/FAP) has been prepared by impregnation method followed by calcination at 900°C. The ratio of impregnation (*RI*) for Na/FAP catalyst was calculated according to equation (1).

$$\mathrm{RI} = \frac{m}{m'} \tag{1}$$

RI: Impregnation ratio
m: Weight of sodium nitrate ($NaNO_3$)
m': Weight of Fluorapatite (FAP)

For each Na/FAP catalyst, an amount of sodium nitrate was dissolved in 50 ml of distilled water and introduced onto 10g of the FAP in a glass flask. The mixture was stirred for 4h at room temperature and evaporated to dryness and calcined for 1 h at 900 °C before use.

The XRD patterns of calcined Na/FAP showed the apparition of new phases (Fig. **1**), so the CaO phase (2θ=32.2; 37.5 and 54.0) is clearly identified.

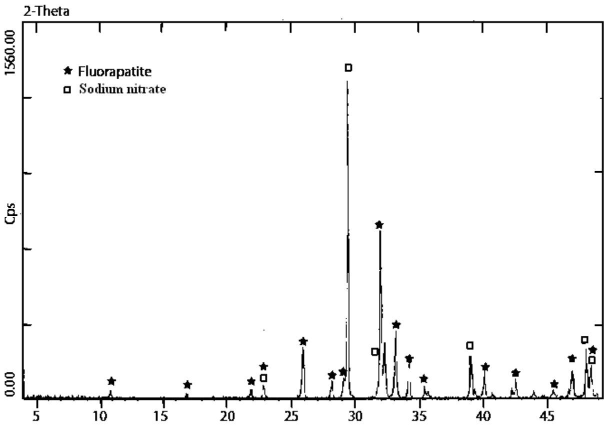

***Figure 1**. X-Ray diffraction of Na/FAP*

Two new phases are probably $CaNaPO_4$ and $Na_2Ca_4(PO_4)_3F$ obtained by an exchange of sodium with calcium. No crystalline phases of Na_2O and CaF_2 were observed.

The infrared spectra of Na/FAP catalyst are run at 150°C under vacuum (Fig. 2).

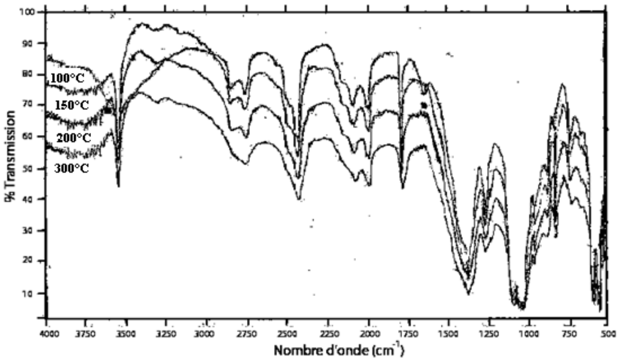

***Figure 2**. Infrared spectra of Na/FAP catalysts calcined at different temperatures.*

The spectrum of dried Na/FAP seems to be a simple combination of nitrate and phosphates bands. It is worth noting that in spectra of both FAP and Na/FAP, no hydroxyls bands are observed in the range of 3000-4000 cm^{-1}.

The calcined material has a very interesting set of peaks for OH groups at high frequency (3710 and 3639 cm^{-1}) and a broad peak at around 1460 cm^{-1} (Fig. 3).

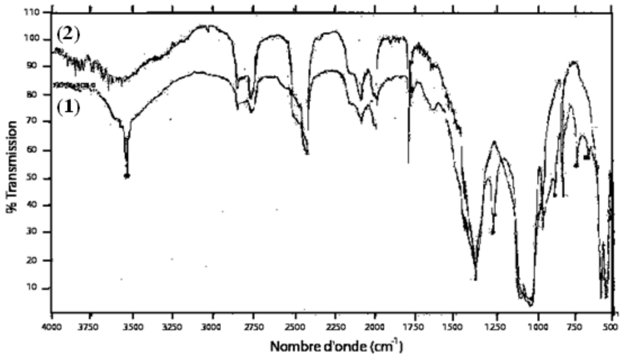

***Figure 3.** Infrared spectra of Na/FAP catalysts calcined (1) and no calcined (2).*

All these peaks are in the spectrum of $Ca(OH)_2$ when heated to 300°C to remove some water. Therefore, it seems that the active species in CaOH type unit, maybe formed by reaction of NaO species with Ca centres.

2.4. General Procedure

The general procedure is as follows: To a flask containing an equimolar mixture (1 mmol) of *p*-Methoxychalcone 1 and Thiophenol 2 in methanol catalyzed by FAP or Na/FAP was added and the mixture was stirred at room temperature until completion of the reaction, as monitored by thin layer chromatography (Fig. 4).

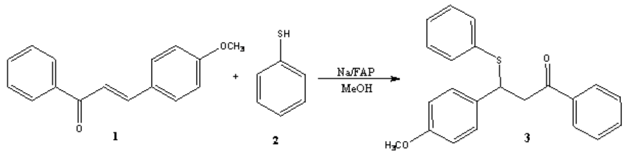

***Figure 4**. Catalytic carbon-sulfur bond formation by Na/FAP catalyst.*

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 ^1H, ^{13}C NMR and IR spectrometry.

2.5. Statistical Analysis

Reaction time (X_1), solvent volume (X_2), catalyst weight (X_3) and impregnation ratio (X_4) were chosen as independent variables and the reaction yield (Y) as dependent output response variable.

Independent variables, experimental range and levels for catalytic carbon-sulfur bond formation are given in Table 1.

***Table 1.** Experimental range and levels*

x	Coded variables (X_i)				
	-2	-1	0	+1	+2
x_1	1	3	5	7	9
x_2	0	0.75	1.5	2.25	3
x_3	30	60	90	120	150
x_4	1/4	1/3	5/12	1/2	7/12

A central composite design, with two replicates at the center point and thus a total of 26 experiments were employed in this study. The center point replicates were chosen to verify any change in the estimation procedure, as a measure of precision property. Experimental plan showing the coded value of the variables together with reaction yield are given in Table 2.

For statistical calculations, the variables X_i were coded as x_i according to the following relationship:

$$x_i = (X_i-X_0)/\delta X \quad (2)$$

The behaviour of the system was explained by the following quadratic equation:

$$Y = \beta_0 + \Sigma\beta_i X_i + \Sigma\beta_{ii} X_i^2 + \Sigma\beta_{ij} X_i X_j \quad (3)$$

The results of the experimental design were studied and interpreted by STATGRAPHICS-Plus computer software to estimate the response of the dependent variable.

***Table 2.** Experimental design and results*

Order	Coded units of variable (Xi)				Reaction yield
	X_1	X_2	X_3	X_4	
01	+1	+1	+1	+1	96
02	+1	+1	+1	-1	63
03	+1	+1	-1	+1	94
04	+1	+1	-1	-1	51
05	+1	-1	+1	+1	95
06	+1	-1	+1	-1	57
07	+1	-1	-1	+1	91
08	+1	-1	-1	-1	48
09	-1	+1	+1	+1	82
10	-1	+1	+1	-1	56
11	-1	+1	-1	+1	74
12	-1	+1	-1	-1	46
13	-1	-1	+1	+1	84
14	-1	-1	+1	-1	52
15	-1	-1	-1	+1	71
16	-1	-1	-1	-1	37
17	+2	0	0	0	83
18	-2	0	0	0	53
19	0	+2	0	0	68
20	0	-2	0	0	51
21	0	0	+2	0	86
22	0	0	-2	0	62
23	0	0	0	+2	84
24	0	0	0	-2	32
25	0	0	0	0	76
26	0	0	0	0	78

3. Results and Discussion

The most important parameters, which affect the efficiency of heterogeneous catalytic of conjugate addition between *p*-methoxychalcone and thiophenol catalyzed by modified fluorapatite are reaction time, solvent volume, catalyst weight and impregnation ratio. In order to study the combined effect of these factors, experiments were performed at different combinations of the physical parameters using statistically designed experiments. The reaction time range studied was between 1 and 9 min, the solvent volume was between 0 and 3 mL, the catalyst weight was between 30 and 150 mg and the impregnation ratio varied between 1/4 and 7/12. Using the experimental results, the regression model equation relating the reaction yield and process parameters was developed and is given in Eqs. (4).

$$\begin{aligned} Y= &+77.0 +6.375*X_1 +2.54167*X_2 +5.04167*X_3 \\ &+15.875*X_4 -1.63542*X_1^2 -3.76042*X_2^2 \\ &- 0.135417*X_3^2 - 4.13542*X_4^2 -0.0625*X_1X_2 \\ &-1.1875*X_1X_3 +2.3125*X_1X_4 -0.5625*X_2X_3 \\ &-1.0625*X_2X_4 -1.1875*X_3X_4 \end{aligned} \quad (4)$$

Apart from the linear effect of the parameter for the reaction yield, the RSM also gives an insight into the quadratic and interaction effect of the parameters. These analyses were done by means of Fisher's '*F*'-test and Student '*t*'-test. The student '*t*'-test was used to determine the significance of the regression coefficients of the parameters. The *P*-values were used as a tool to check the significance of each of the interactions among the variables, which in turn may indicate the patterns of the interactions among the variables.

In general, larger the magnitude of *t* and smaller the value of *P*, the more significant is the corresponding coefficient term. The regression coefficient, *t* and *P* values for all the linear, quadratic and interaction effects of the parameter are given in Table 3.

Table 3. *Regression variance analysis of the model*

Source of variation	Coefficient	ν	F_{exp}	Significance test
Regression	-	14	25.9203	***
β_0	77	01	-	-
β_1	6.375	01	41.87	***
β_2	2.54167	01	6.66	*
β_3	5.04167	01	26.19	***
β_4	15.875	01	259.64	***
β_{11}	-1.63542	01	2	NS
β_{12}	-0.0625	01	0	NS
β_{13}	-1.1875	01	0.97	NS
β_{14}	2.3125	01	3.67	NS
β_{22}	-3.76042	01	10.6	***
β_{23}	-0.5625	01	0.22	NS
β_{24}	-1.0625	01	0.78	NS
β_{33}	-0.13541	01	0.01	NS
β_{34}	-1.1875	01	0.97	NS
β_{44}	-4.13542	01	12.81	***
Residue	-	11	-	-
Total	-	25	-	-

*** : $p \leq 0{,}01$; ** : $p \leq 0{,}025$; * : $p \leq 0{,}05$; NS : No significant.

It was observed that the linear terms (X_1, X_2, X_3 and X_4) and the squared terms (X_2^2 and X_4^2) were significant model terms whereas the squared terms (X_1^2 and X_3^2) and the interaction terms (X_1X_2, X_1X_3, X_1X_4, X_2X_3, X_2X_4 and X_3X_4) were insignificant to the response.

From the analysis of variance for model of catalytic carbon-sulfur bond formation, the model F-value of 25.92 implied that the model was significant. Values of Prob. > F (F0.01 (14, 11) = 4.29) less than 0.01 indicated that the model terms was significant.

The final empirical model in term of coded factors after excluding the insignificant terms for reaction yield is shown in Eq. (5):

$$\begin{aligned} Y = &77 +6.375*X_1 +2.54167*X_2 +5.04167*X_3 \\ &+15.875*X_4 -3.76042*X_2^2 - 4.13542*X_4^2 \end{aligned} \quad (5)$$

Positive sign in front of the terms indicates synergistic effect, whereas negative sign indicates antagonistic effect.

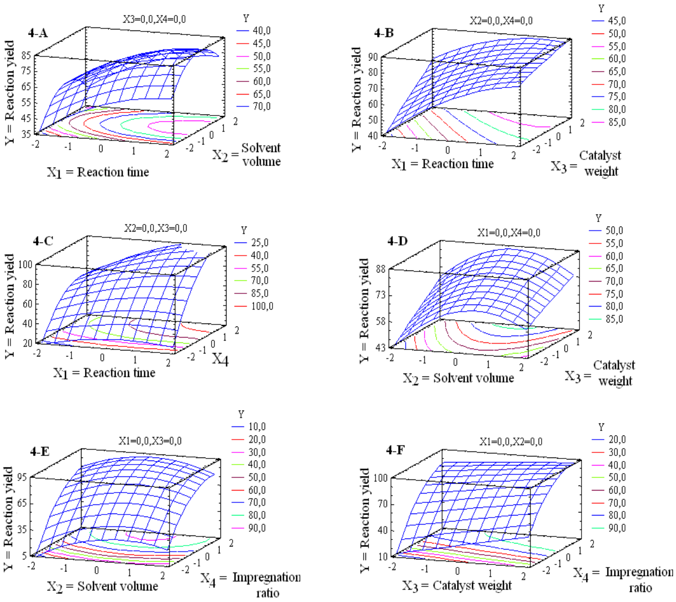

Figure 5*. Response surface graphs for interactions between independent variables with other variable being at fixed level.*

Interactions between independent variables are shown in three-dimensional surface plots with other variable being at fixed level (Fig. 5 A-F).

Fig. 5-A shows the interaction between reaction time (X_1) and solvent volume (X_2) at constant value of the catalyst weight (X_3=0) and the impregnation ratio (X_4=0). Interaction between reaction time (X_1) and catalyst weight (X_3) at constant value of the solvent volume (X_2=0) and the impregnation ratio (X_4=0) is shown in Fig. 5-B.

Fig. 5-C shows the interaction between reaction time (X_1) and impregnation ratio (X_4) at constant value of the solvent volume (X_2=0) and the catalyst weight (X_3=0). Interaction between solvent volume (X_2) and catalyst weight (X_3) at constant value of the reaction time (X_1=0) and the impregnation ratio (X_4=0) is shown in Fig. 5-D.

Fig. 5-E shows the interaction between solvent volume (X_2) and impregnation ratio (X_4) at constant value of the reaction time (X_1=0) and the catalyst weight (X_3=0). Interaction between catalyst weight (X_3) and impregnation ratio (X_4) at constant value of the reaction time (X_1=0) and the solvent volume (X_2=0) is shown in Fig. 5-F.

The main objective of this research is to determine the best reaction conditions to heterogeneous catalytic of conjugate addition between *p*-methoxychalcone and thiophenol catalyzed by modified fluorapatite. 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:

$$Y = \text{high reaction yield} \tag{6}$$

- Constraints on the parameters *X*:

$$-\alpha_i < X_i < +\alpha_i \quad i=1,2,3,4 \tag{7}$$

The investigation of equation 5 showed that, if X1=0.5, X2=0, X3=0.5 and X4=1; the value predict from the results using response surface model is 94%.

The experimental checking in this point, i.e. under the optimum reaction conditions such as: reaction time=6min, solvent volume=1.5 mL, catalyst weight=105mg and impregnation ratio=1/2 with high reaction yield 95%, confirms this result.

The use of Na/FAP heterogeneous catalyst is particularly interesting since it's regenerated by calcinations at 900°C during 15 min, and after five successive recoveries, product 3 was obtained with same yield. Thus, we estimate that the surface of the synthetic phosphate Na/FAP catalyst presents certainly multicatalytic active sites. The basic sites (F^- of CaF_2 group and oxygen of PO_4, CaO and Na_2O group) enhance the donors nucleophilicity. The acidic sites (Ca^{2+}, Na^+ and phosphorus PO_4 group) probably increases the enone moiety polarization. Consequently, the carbon-sulfur bond formation is accelerated and the sulfanyl product is obtained by the transfer of proton. The products of undesirable side reactions resulting from 1,2 addition, polymerization and bis-addition are not observed.

4. Conclusion

The present study clearly demonstrated the high heterogeneous catalytic activity for synthetic phosphate Na/FAP in conjugate addition between *p*-methoxychalcone and thiophenol. This study clearly showed that response surface methodology was one of the suitable methods to optimize the best operating conditions to maximize the yield reaction condition. Graphical response surface was used to locate the optimum point.

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