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

Younes Abrouki, Abdelkader Anouzla, Hayat Loukili, Rabiaa Lotfi, Ahmed Rayadh, My Abdellah Bahlouli, Saïd Sebti, Driss Zakarya and Mohamed Zahouily

1Department of Research, Faculty of Science and Technology, University Hassan II, Mohammedia, Morocco.
2Department of Chemistry, Faculty of Science Ben M’Sik, University Hassan II, Casablanca, Morocco.

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 \( p \)-methoxyxalchene 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 \( (X_1) \), solvent volume \( (X_2) \), catalyst weight \( (X_3) \) and impregnation ratio \( (X_4) \) on the reaction yield \( (Y) \) was studied and optimized using response surface methodology.

Keywords

Conjugate addition,
Fluorapatite,
Heterogeneous catalyst,
Response optimization,
Central Composite Design.

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 hydrotralcite [2], alumina [3], montmorillonite [4], zeolites [5], natural phosphate [6], animal bone meal [7], hydroxyapatite [8], synthetic diphosphate \( \text{Na}_2\text{Ca}_2\text{P}_2\text{O}_7 \) [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 \( \text{R} = \text{C}_6\text{H}_{4}\) 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 \( p \)-methoxyxalchene and thiophenol has been used as model reaction.

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 \( S=15.4 \text{ m}^2\text{g}^{-1} \). The total pore volume was calculated by the BJH method at \( P/P_0=0.98 \) and found to be \( V_t=0.0576 \text{ cm}^3\text{g}^{-1} \).

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 \( (R_I) \) for Na/FAP catalyst was calculated according to equation (1).

\[
R_I = \frac{m}{m'}
\]

\( R_I \): Impregnation ratio
\( m \): Weight of sodium nitrate \( (\text{NaNO}_3) \)
\( m' \): Weight of Fluorapatite \( (\text{FAP}) \)

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, so the \( \text{CaO} \) phase \( (2\theta=32.2; 37.5 \) and 54.0) is clearly identified. Two new phases are probably \( \text{CaNaPO}_4 \) and \( \text{Na}_2\text{Ca}_2\text{(PO}_4)_2\) obtained by an exchange of sodium with calcium. No crystalline phases of \( \text{Na}_2\text{O} \) and \( \text{CaF}_2 \) were observed.
The infrared spectra of Na/FAP catalyst are run at 150°C under vacuum (Fig. 1). 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.

Figure 1. Infrared spectra of Na/FAP catalysts calcined at different temperatures.

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. 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 Ca(OH)₂ unit, maybe formed by reaction of NaO species with Ca centres.

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

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. 3).

Figure 3. Catalytic carbon-sulfur bond formation by Na/FAP.

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, ¹³C NMR and IR spectrometry.

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 for catalytic carbon-sulfur bond formation.

<table>
<thead>
<tr>
<th>Natural variable</th>
<th>Unit</th>
<th>Coded variables ($X_i$)</th>
<th>Reaction yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>$X_1$ = Reaction time</td>
<td>min</td>
<td>-2 -1 0 +1 +2</td>
<td>96</td>
</tr>
<tr>
<td>$X_2$ = Solvent volume</td>
<td>ml</td>
<td>-2 -1 0 +1 +2</td>
<td>63</td>
</tr>
<tr>
<td>$X_3$ = Catalyst weight</td>
<td>mg</td>
<td>-2 -1 0 +1 +2</td>
<td>94</td>
</tr>
<tr>
<td>$X_4$ = Impregnation ratio</td>
<td>-</td>
<td>-2 -1 0 +1 +2</td>
<td>51</td>
</tr>
</tbody>
</table>

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:

$$x_i = \frac{X_i - X_0}{\delta X} \quad (2)$$

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

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

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

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

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
(second order polynomial) relating the reaction yield and
process parameters was developed and is given in Eqs. (4).
\[ Y = + 77.0 + 6.375*X_1 + 2.54167*X_2 + 5.04167*X_3 + 15.875*X_4 +
-1.63542*X_1^2 - 3.76042*X_2^2 - 0.135417*X_1^2 - 4.13542*X_2^2
-0.0625*X_1*X_2 - 1.1875*X_1*X_4 + 2.3125*X_1*X_3 - 0.5625*X_1^3 +
-1.0625*X_2*X_4 - 1.1875*X_2^2
\]
(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 regres-
sion 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 r 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>
<thead>
<tr>
<th>Table 3. Regression variance analysis of the model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source of variation</td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td>Regression</td>
</tr>
<tr>
<td>β0</td>
</tr>
<tr>
<td>β1</td>
</tr>
<tr>
<td>β2</td>
</tr>
<tr>
<td>β3</td>
</tr>
<tr>
<td>β11</td>
</tr>
<tr>
<td>β12</td>
</tr>
<tr>
<td>β13</td>
</tr>
<tr>
<td>β14</td>
</tr>
<tr>
<td>β22</td>
</tr>
<tr>
<td>β23</td>
</tr>
<tr>
<td>β24</td>
</tr>
<tr>
<td>β33</td>
</tr>
<tr>
<td>β34</td>
</tr>
<tr>
<td>β44</td>
</tr>
<tr>
<td>Residues</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

It was observed that the linear terms (X_1, X_2, X_3 and X_4)
and the squared terms (X_1^2 and X_2^2) were significant model
terms whereas the squared terms (X_1^2 and X_2^2) and the
interaction terms (X_1*X_2, X_1*X_3, X_2*X_3, X_2*X_4 and X_3*X_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):
\[ Y = 77 + 6.375*X_1 + 2.54167*X_2 + 5.04167*X_3 + 15.875*X_4
-3.76042*X_1^2 - 4.13542*X_2^2
\]
(5)

Positive sign in front of the terms indicates synergistic effect,
whereas negative sign indicates antagonistic effect. Interac-
tions between independent variables are shown in three-di-
imensional surface plots with other variable being at fixed
level (Fig. 4 A-F).

Fig. 4-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. 4-B.

Fig. 4-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. 4-D.

Fig. 4-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. 4-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:

\[ Y = \text{high reaction yield} \]  

Constraints on the parameters: 

\[ a_i < X_i < b_i, \quad i = 1, 2, 3, 4 \]  

The investigation of equation 5 showed that, if \( X_1 = 0.5, \) \( X_2 = 0, \) \( X_3 = 0.5 \) and \( X_4 = 1; \) 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 = 6 min, solvent volume = 1.5 mL, catalyst weight = 105 mg 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 catalysed presents certainly multicatalytic active sites. The basic sites (F of CaF\(_2\) group and oxygen of PO\(_4\), CaO and Na\(_2\)O 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.

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.

Acknowledgements

We are grateful to Mr. Hamid Dhimane and Mr. Marc David of Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques, Université René Descartes Paris-France, for his help with data analysis.

References


