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Isolation, synthesis and optimization of cyclopropanation process of 4-allyl-2-methoxyphenol

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Abstract

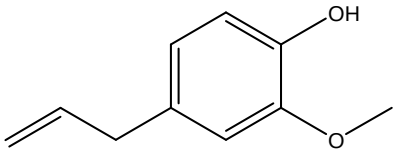
The synthesis of 4-((2,2-dichlorocyclopropyl)methyl)-2-methoxyphenol 2 have been accomplished by using cyclopropanation process and Reponse Surface Methodology [1,2]. This methodology was used to determine the optimal conditions for the cyclopropanation reaction of eugenol 1. The reaction time (X1) and the ratio of the reaction mixture's solvent (X2) were the two investigated factors. The statistical analysis of this study indicates that both of these factors had significant effects on the cyclopropanation yield.

The central composite design showed that polynomial regression models were in good agreement with the experimental results of the coefficient determination (0.95) of product 2 yield. The optimal conditions were 17.44 and 5.78 hours. In such condition, the predicted yield of the product 2 was 43.96%.

Keywords: Eugenol; 4-((2,2-dichlorocyclopropyl)methyl)-2-methoxyphenol; Central composite design; Optimization experiment.

1. Introduction

Clove oil (CO) is an essential oil from the dried flower buds, leaves and stem of the tree Syzygium aromaticum (Eastern Hemisphere) or Eugenia caryophyllata and Eugenia aromaticum (Western hemisphere) [Schmid R. 1972]. It has been used for centuries as anesthetic for toothaches, headaches and joint pain [Shelef L. A. 1983; Soto C. G. et al. 1995]. Clove has received attention as an ideal fish anaesthesic [Ackerman J. L. and Bellwood D. R. 2002; Roubach R. et al. 2005] and it has been used as a fragrant and flavoring agent in a variety of food and cosmetic products [Atsumi T. et al. 2001, Ito M. et al. 2005]. ¶However, irritation towards the mucosa and skin, pungent taste, volatility, light sensitivity and poor water solubility make it unsuitable to use as such.
Eugenol (EG) 1 (4-allyl-2-methoxyphenol) is the principal constituent of the essential CO, being 90% - 95% of the total oil amount [Briozzo J. L. et al. 1989; Gülçin I. et al. in press]. It has a strong phenolic smell and sharp acrid taste [Mouchrek V. 2000; Ozturz A. and Ozbek H. 2005] and its chemical structure is represented in Figure 1.



4-allyl-2-methoxyphenol

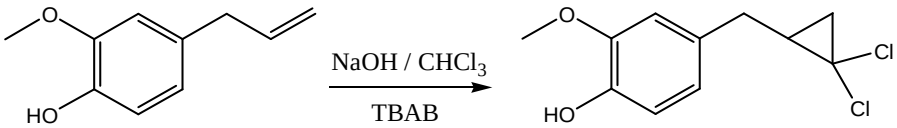
Figure 1. Chemical structure of Eugenol isolated from the essential oil from *Eugenia Caryophyllata*

This phenolic compound has shown several biological activities such as anti-inflammatory activity by inhibiting the enzyme cyclooxygenase II [Son K. H. et al. 1998], analgesic activity due to selective binding at capsaicin receptor [Ohakubo T. and Shibata M. 1997], anti-oxidative activity and anti-bacterial activity against both gram positive and gram negative microorganisms. Clove Oil (CO) can be used for acne, bruises, burns and cuts, keeping infection at bay and as a pain reliever. It helps with toothache, mouth sores, rheumatism and arthritis. It

is beneficial to the digestive system, effective against vomiting, diarrhea, flatulence, spasms and parasites, as well as bad breath. Clove Oil is valuable for relieving respiratory problems, like bronchitis, asthma and tuberculosis. The disinfecting property is useful in cases of infectious diseases [Ou H. C. et al. 2006; Nam H. and Kim M.M. 2013; Kalemba D. and Kunicka A. 2003].

The objectives of this work is the optimization and study the effect of temperature, reaction time and the ratio of solvent to raw material on the yield of the cyclopropanation of eugenol extracted from clove. Using the response surface methodology (RSM)), using a two-factor five-level central composite design (CCD). The enormous importance of functionalized cyclopropanes, in various scientific fields, lies in their diverse biological activity [Enayati, A. A. et al. 2003; Lynd, A. et al. 2005 ; Takken, W. 2002 ; Khambay, B. P. S. 2002 ; Darriet, F. et al. 2004] and their usefulness as valuable building blocks in organic synthesis [Gazzaeva, R. et al. 2005 ; Gnad, F. and Rieser, O. 2003; Pietruszka, 2003; Bakunov, S. A. et al. 1994; Lee, P. H. et al. 1993; Hammond, G. B. et al. 1990 ; Arlt, D. et al. 1981]. The dichlorocyclopropanation reaction was achieved using phase-transfer catalysis technique. The primary advantages of using phase-transfer catalysis are to obtain a large conversion, high reaction rate and selectivity at moderate reaction conditions [Jayachandran, P. and Wang, M.-L. 2001; Wang, M.-L. et al. 2003; Sirovski, F. et al. 2003 ; Bachowska, B. and Zujewska, T. 2001]. It is interesting to note that powdered KOH or NaOH/BTEAC/CHCl3 has been suggested as a very effective CCl2 precursor [Juliá, S. and Ginebreda, A. 1977 ; Juliá, S. and Ginebreda, A. 1980]. A comparison with the original Makosza method showed similar yields, but the process with solid base was proved to be faster [Bachowska, B. and Zujewska, T. 2001; Juliá, S. and Ginebreda, A. 1977; Juliá, S. and Ginebreda, A. 1980].

We have reported the synthesis of new functionalized cyclopropanes from eugenol 1. This synthesis involves a periselective gem-dihalocyclopropanation reaction. Our strategy consists in a dichlorocyclopropanation of eugenol 1 gave the new product 4-((2,2-dichlorocyclo-propyl)methyl)-2-methoxyphenol 2. In this section we follow an experimental design by changing the volume of chloroform added and the reaction time to optimize the reaction conditions. Dichlorocarbene was used as the carbene component. It was generated by the adapted method to eugenol, reaction of NaOH with chloroform at room temperature in the presence of Tertiobutylammoniumbromid (TBAB) as the phase transfer catalyst (scheme1).



1 **2**

Scheme 1: reaction cyclopropanation avec le 4-((2,2-dichlorocyclopropyl)methyl)-2-methoxyphenol (eugénol)

2. Materiel and method

2.1. Extraction of eugenol

Commercially available plant material (buds) was purchased for the essential oil extraction. The buds of Eugenia caryophyllata were extracted by steam distillation for 4h.

The distillation was extracted with diethyl ether, dehydrated with anhydrous sodium sulfate and solvent removed and by evaporation using a rotator evaporator at 40°C.

The residual oil obtained was used for chemical analysis, further purification and biological assays. Extracted oil was subjected to silica gel column chromatography (Merck, Germany, 3 (21cm, 60g)) with the eluent of *n*-hexane; ethyl acetate (10: 1). The eluate was collected in 30 fractions of 30ml, Fractions collected were evaporation and the residual obtained is colorless oil was identified by ^{1}HNMR (300 MHz, $CDCl_3$), ^{13}C-NMR (125MHz, $CDCl_3$).

2.2. Cyclopropanation of Eugenol

Eugenol (500 mg, 3.048 mmol) was dissolved in chloroform (the volume of the chloroform depending on experience level) and 28.06 mg (0.087 mmol) of TBAB. It adds drop wise with stirring a solution of $NaOH/H_2O$ (5g/5ml). This reaction mixture was then heated under reflux for several hours (depending on the level of

experience). After cooling, the mixture was poured into 25ml of H_2O and extracted with ether in a separation funnel. The organic phase obtained was laved three times with water or a saturated solution of NaCl then was dehydrated with anhydrous sodium sulfate and filtered. The organic phase was evaporated and the residual obtained dried and passed through silica gel column. The product obtained after purification, the colorless oil was identified by ^{1}HNMR (300 MHz, $CDCl_3$).

4-((2,2-dichlorocyclopropyl)methyl)-2-methoxyphenol:

^{1}HRMN ($CDCl_3$, 300 MHz) : (ppm) 7-6.5 (m, 3H, CH-Ar), 5.14 (S, 2H, CH_2O), 3.91 (S, 3H, CH_3O), 2.96-2.71 (m, 2H, CH_2Ar), 1.7-1.64 (m, 1H, CH), 1.26-1.21 (m, 2H, CH2).

^{13}CRMN ($CDCl_3$, 300 MHz) : (ppm) 149.7 (ArO), 146.8 (C-OCH_3), 137.3 (Ar-C), 132.6 (CCl), 120.1 (CH'3'), 114.3 (CH5'), 112.2 (CH4'), 71.2 (CH_2O), 56.1 (CH_3O), 35.5 (CH_2Cl), 31.6 (CH), 26.7 (CH_2Ar).

2.3. *Experimental design*:

The reaction parameters were optimized using response surface methodology. The central composite design (CCD) was employed in this regard. The range and center point values of three independent variables presented in Table 1 were based on the results of preliminary experiments.

Table 1: Independent variables and their levels used for central composite rotatable design

	-1.68	-1	0	1	1.68
the reaction time (h)	3	5.78	12.5	19.22	22
Ratio of solvent to raw material	2.5	5.06	11.25	17.44	20

CCD in the experimental design consists of eight factorial points, six axial points and six replicates of the central point (Table 2). Reaction time (X_1) and ratio of solvent to raw material (X_2) were chosen for independent variables.

Yield of 4-((2,2-dichlorocyclopropyl)methyl)-2-methoxyphenol was selected as the response for the combination of the independent variables given in (Table 2). Experimental runs were randomized to minimize the effects of unexpected variability in the observed responses.

The variables were coded according to the equation:

$$x_i = (X_i - X_0)/\Delta X \qquad (1)$$

Where x_i is the (dimensionless) coded value of the variable X_i, X_0 is the value of X_i at the centre point, and ΔX is the step change. Table 3 shows the actual design of experiments. The behavior of the system was explained by the following second degree polynomial equation:

$$Y = A_0 + \sum_{i=1}^{2} A_i X_i + \sum_{i=1}^{2} A_{ii} X_i^{\,2} + \sum_{i=1}^{2} \sum_{j=i+1}^{2} A_{ij} X_i X_j \qquad (2)$$

Table 2: The central composite experimental design (in actual level of three variables) employed for extraction of arylallyl

std	Time	Ratio of solvent to raw material	Arylallyl yield (%)	
	X_1	X_2	Experimental	Predicted
1	-1	-1	38.41	37.56
2	1	-1	36.25	36.69
3	-1	1	43.31	43.96
4	1	1	33.8	35.74
5	-1.414	0	37.07	37.43
6	1.414	0	32.46	31.00
7	0	-1.414	40.32	40.83
8	0	1.414	46.3	44.69
9	0	0	32.1	33.44
10	0	0	33.3	33.44
11	0	0	35.3	33.44
12	0	0	33.3	33.44
13	0	0	33.2	33.44

2.4. Statistical analyses

Analysis of the experimental design and calculation of predicted data were carried out using software Design-Expert v.7.0.0 to estimate the response of the independent variables. Subsequently, three additional confirmation experiments were conducted to verify the validity of the statistical experimental strategies.

3. Results and discussion

3.1. Preliminary study

Single-factor experimental designs (reaction times, and ratio of solvent to raw material) were carried out before RSM experiments, in order to determine the experimental fields.

3.1.1. Time

The effect of different time on cyclopropanation yield of 4-((2,2-ichlorocyclopropyl)methyl)-2-methoxyphenol is shown in Figure 2. The reaction yield of cyclopropanation slowly decreased with increasing time until reaching 25 (s/v), after which it remained relatively stable.

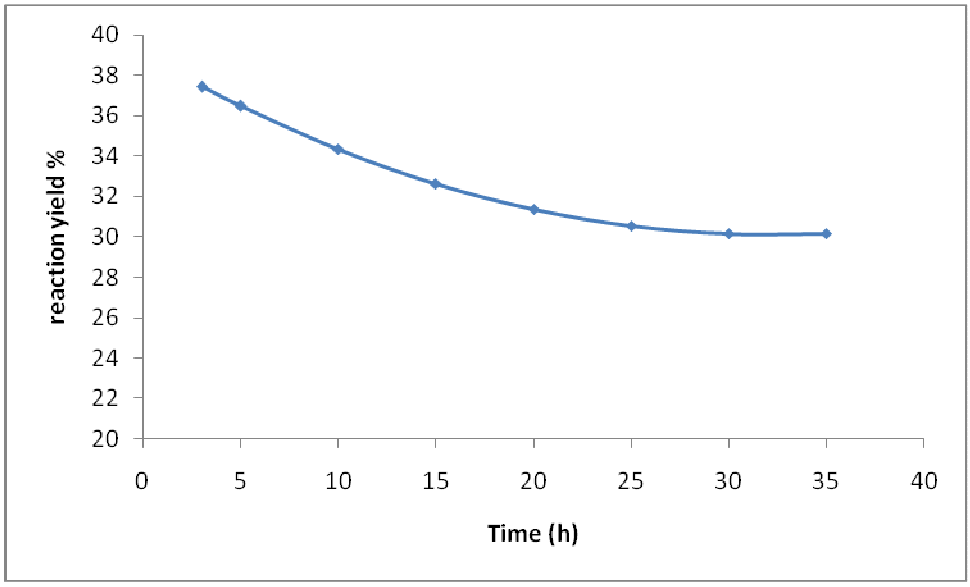


Figure 2. Effect of time on reaction yield.

3.1.2 Ratio of solvent to raw material

The effect of different ratio of solvent to raw material on cyclopropanation yield of product is shown in Figure 3. The cyclopropanation was carried out with ratios which vary between 5 and 30 under the following conditions of extraction: Time = 14h.

Figure 3 shows that the 4-((2,2-dichlorocyclopropyl)methyl)-2-methoxyphenol yield increased significantly from 33% to 45% as the ratio of solvent to the raw material increased from 10 to 20. However, when the ratio continued to increase, the reaction yields no longer changed.

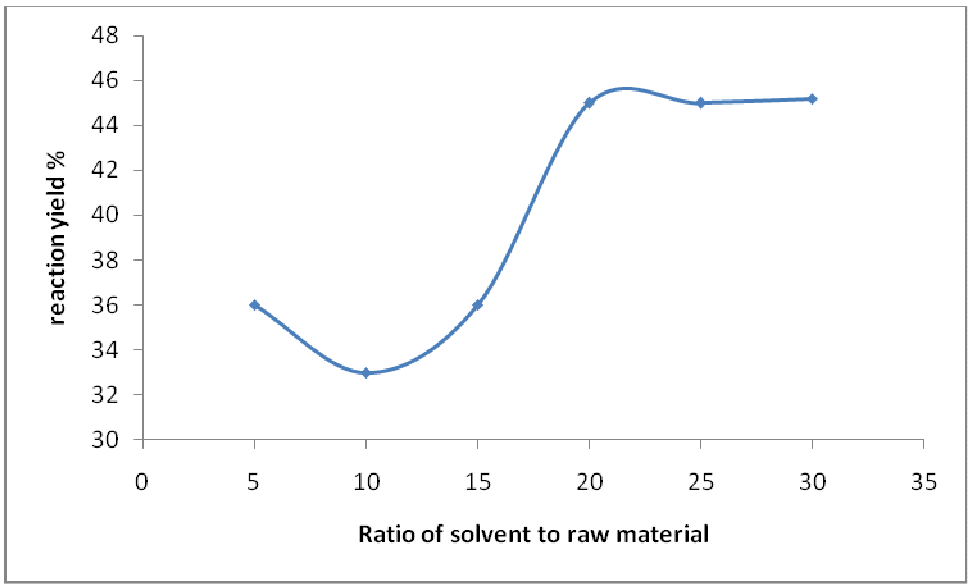


Figure 3. Effect of ratio of solvent to raw material on reaction yield.

3.2. Predicted model and statistical analysis

Table 3 shows the process variables and experimental data. The results of the analysis of variance, goodness-of-fit and the adequacy of the models are summarized. The percentage yield ranged from 32.1% to 46.3%. The maximum value was found at reaction time 12.5h and ratio of solvent to raw material 20. The application of

RSM offers, based on parameter estimates, an empirical relationship between the response variable (cyclopropanation yield of 4-((2,2-dichlorocyclopropyl)methyl)-2-methoxyphenol) and the test variables under consideration. By applying multiple regression analysis on the experimental data, the response variable and the test variables are related by the following second-order polynomial equation (2):

$$Y=33.44 -2.27 * X_1 +1.36 * X_2 -1.84 * X_1 * X_2 +0.39 * X_1 * X_1 +4.66 * X_2 * X_2 \quad (2)$$

Where $X_1$and X_2 were the coded values of the test variables: extracting time (h) and ratio of solvent to raw material, respectively.

The statistical significance of regression equation was checked by F-test, and the analysis of variance (ANOVA) for response surface quadratic polynomial model was done by the Design-Expert v.7.0.0 software. The ANOVA of quadratic regression model demonstrated that the model was highly significant. And the Fisher's F-test had a very high model F-value (19.88) and a very low P-value ($P < 0.0001$). The value of R^2Adj (0.9342) for Eq. (3) is reasonably close to 1, and indicates a high degree of correlation between the observed and predicted values. A very low value of coefficient of the variation (C.V.) (4.08 %) clearly indicated a very high degree of precision and a good deal of reliability of the experimental values. The F-value (2.55) and P-value (0.1941) of lack-of-fit implied the lack-of-fit was not significant relative to the pure error. It indicates that the model equation is adequate for predicting the yield of 4-((2,2-dichlorocyclopropyl)methyl)-2-methoxyphenol under any combination of values of the variables. The coefficient estimates of model equation, along with the corresponding P-values, were presented in Table 3. The P-values are used as a tool to check the significance of each coefficient, which also indicate the interaction strength between each independent variable. When value of ''probability > F" is less than 0.05, the model terms is significant.

It can be seen from this table that the linear coefficients (X_1, X_2), a quadratic term coefficient (X_2) and cross product coefficients (X_1*X_2) were significant, with very small P values ($P < 0.01$). The other term coefficient (X_1*X_1) are not significant ($P > 0.05$)

Table 3: Test of significance for regression coefficients

Effect	Coefficient estimate	Standard error	F-value	P value
X_1	-2.27	0.53	18.59	0.003
X_2	1.36	0.53	6.68	0.036
X_1*X_1	0.39	0.57	0.47	0.5140
X_2*X_2	4.66	0.57	67.92	<0.0001
X_1*X_2	-1.84	0.75	6.07	0.043

3.3. Analysis of response surfaces

The effects of the two factors as well as their interactive effects on the 4-((2,2-dichlorocyclopropyl)methyl)-2-methoxyphenol yield are shown in figure 4 : Response surface plot and contour plot of extraction time and the ratio of solvent to material of effect of reaction time (X_1) and cyclopropanation ratio of solvent of raw material (X_2) on response. As can be seen, enhancing the reaction time (X_1) from 3 to 22h could decrease the arylallyl yield. Enhancing the ratio of solvent of raw material (X_2) from 2.5 to 20 could also increase the 4-((2,2-dichlorocyclopropyl)methyl)-2-methoxyphenol yield. It is concluded that a high cyclopropanation yield could be obtained by combining appropriate ratio of liquid to solid (X_2) and extraction time (X_1).

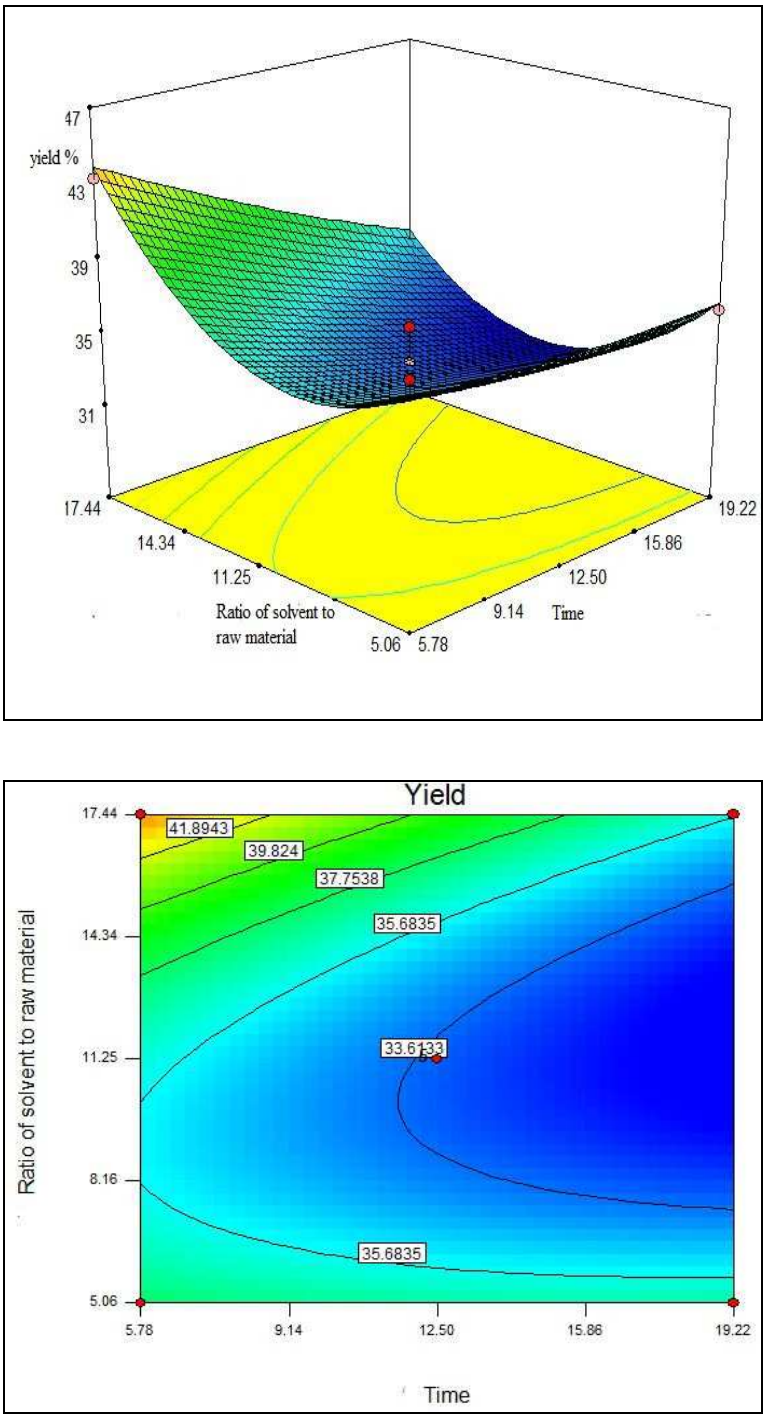


Figure 4. Response surface plot and contour plot of reaction time and the ratio of solvent to material and their mutual interactions on the yield of arylallyl.

4. Conclusion

In this study, dual RSM was successfully applied to determine the reaction conditions for 4-((2,2-dichlorocyclopropyl)methyl)-2-methoxyphenol. A set of optimum reaction conditions were established. Furthermore, under optimized conditions the experimental values achieved agrees well with the predicted data. According to the optimum model the cyclopropanation yield could exceed 43.96%.

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