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Highly efficient and green synthesis of diacylphloroglucinol over treated natural zeolite mordenite and the optimization using response surface method (RSM)

Wahyu Eko Prasetyo^a, Triana Kusumaningsih^b (b), and Maulidan Firdaus^c (b)

^aDepartment of Chemistry, Graduate School, Sebelas Maret University, Surakarta, Indonesia; ^bDepartment of Chemistry, Faculty of Mathematics and Natural Sciences, Sebelas Maret University, Surakarta, Indonesia; ^cResearch Group of Synthesis and Material Functionalization, Sebelas Maret University, Surakarta, Indonesia

ABSTRACT

Herein, we report a greener and highly efficient route for the Friedel-Craft acylation of phloroglucinol over Indonesian treated natural zeolite mordenite (nHZMOR) catalyst to provide value-added diacylphloroglucinol derivatives under solvent-free conditions. The nHZMOR showed a high catalytic performance in Friedel-Craft acylation of a phloroglucinol reaction, and diacylphloroglucinol derivatives were obtained in excellent yields. The advantages of the use of this catalyst are solvent-free, shorter reaction time, high yields, and its recyclable ability. Easy catalyst separation was demonstrated through filtration and reused several times without noticeably decreasing its catalytic activity; however, with regeneration treatment, its catalytic performance can be improved. The effect of catalyst loading, reaction temperature, solvent effect and reaction time has been extensively studied. In addition, the chemical process was enhanced by the use of coupling automated synthesis equipment with the Response Surface Method (RSM) to optimize the Friedel-Craft acylation reaction. Also, a reasonable reaction mechanism had presented.

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KEYWORDS

Diacylphloroglucinol; green synthesis; natural zeolite mordenite catalyst; solvent-free

GRAPHICAL ABSTRACT



Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/lsyc.

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CONTACT Triana Kusumaningsih 🕲 triana_kusumaningsih@staff.uns.ac.id 💽 Department of Chemistry, Faculty of Mathematics and Natural Sciences, Sebelas Maret University, Jl. Ir. Sutami No.36A, Surakarta, 57126, Indonesia; Maulidan Firdaus 🖾 maulidan@mipa.uns.ac.id 💽 Research Group of Synthesis and Material Functionalization, Sebelas Maret University, Jl. Ir. Sutami 36A, Kentingan, Surakarta, 57126, Indonesia

Introduction

Diacylphloroglucinol^[1,2] is a privileged natural phenolic compound, which has broad biological properties, namely antibacterial,^[3] antibiotic,^[4] antifungal,^[5] anticancer and anti-HIV.^[6–8] Additionally, diacylphloroglucinol is a vital synthon to obtain of a various crucial phenolic compound such as dimeric acylphloroglucinol.^[7,9] Naturally occurring diacylphloroglucinol compounds are widely found from natural sources such as plants, microbes, and marine organisms.^[10] Diacylphloroglucinol can be chemically synthesized through the Friedel-Craft acylation reaction and promoted by Brønsted or Lewis acid catalyst. Employing the Friedel-Craft reaction is the main strategy for making aromatic ketones.^[11–14]

Previous studies reported that the most electrophilic acylation of phloroglucinol was catalyzed by various conventional homogenous catalysts such as Lewis acid (AlCl₃, BF₃and ZnCl₂) or Brønsted acid catalyst (HCl, HF, and H₂SO₄).^[4,15,16] In particular, all of the previously mentioned strategies have limitations such as strict reaction conditions, the use of dangerous and frequently expensive acid catalysts and solvents that normally produce a large amount of toxic waste, longer reaction times, and low or moderate yields.^[7,17] In addition, another problem might appear from the use of metal halides that cause difficulties linked with the formation of strong complex among the product and the metal halide which avoids in excess of catalyst.^[18] In terms of the "green revolution", methanosulfonic (MSA) catalyst has been employed successfully as a superior greener homogenous catalyst replacing the previous Friedel-Craft acylation conventional catalyst.^[2,7,19] Despite its benefits, utilization of homogeneous catalytic systems for these reactions cause numerous issues such as formed contaminants along preferred products and difficulty in recovery, as well as difficulty of the catalyst separation and regeneration process.^[20,21] A new and extensive synthetic method must involve as an element of environmental and ecological point of view.^[22-24] By designing and developing robust solid catalysts is the better one strategy of a fascinating and challenging ambition in Friedel-Craft acylation which recently the most attempts have been focused toward the use of a solid catalyst.^[25-29]

Utilization of zeolite as a catalyst in Friedel-Craft reactions is currently a popular research area.^[30-32] Zeolite has been intensively evaluated as a heterogenous catalyst for acylation or benzylation of various aromatic compounds.^[30,32,33] Zeolite's three-dimensional cavities can provide a selective environment, which allows a specific chemical reaction to occur. Additionally, its polar nature properties make it suitable for use as a solid acid catalyst under solvent-free conditions. Representing reaction without the use amount of solvent is not only a strategy for diminishing waste and energy intake, but also offers synthetic advantages in terms of effortlessness, yield, and selectivity.^[34,35] Nevertheless, the use of synthetic zeolites as catalysts are expensive, the presence of homogeneous micropores and relatively high acidity, which encourage morph selectivity. However, the small size homogeneous micropores entail a low rate of intracrystalline diffusion between products and reactants, also the high possibility formation of pore-clogging. To overcome these problems, mordenite is treated with acids causing the dealumination triggers the mesoporous structure development process, which and acidity decrement.[36,37]

The exploration of "natural" zeolite is one of the best strategies for minimizing excessive cost. Indonesian natural zeolite resources have been revealed to be more than 205.82 million tons of which almost all are distributed in Java Island, especially in Wonosari, Yogyakarta Regency.^[38–40] This zeolite tuff was reported predominantly by Mordenite type zeolite (nZMOR) with a higher SI/Al ratio and several impurities.^[41] Because nZMOR has a different character to synthetic zeolite, a treatment for improving its catalytic performance is essential.^[42–45] Its catalytic properties can be improved physically, chemically and with a combination of both approaches such as reducing the impurities or changing the Si to Al ratio through the dealumination process or ion exchange of the mobile cations.^[38,42,46,47] In most previous literature, the Friedel-Craft acylation reaction with zeolite dominantly catalyzed by its Brønsted active site. Thus, treatment for nZMOR processed by ion exchange of their mobile cations with NH₄⁺ and calcined to form natural zeolite with dominantly Brønsted active site (nHZMOR).^[26,48,49]

In this work, we investigated the synthesis of diacylphloroglucinol derivative compounds employing natural active zeolite (nHZMOR) as a catalyst without the use of solvent. To the best of our knowledge, diacylphloroglucinol synthesis via Friedel-Craft catalyzed by treated natural zeolite has not been reported. Furthermore, instead of attempting widespread and optimization, the progress of quickly automated process research strategies for Friedel-Craft acylation reaction optimization combined with the statistical design of experimental (DoE) has been studied. The DoE method has been adopted and evaluated in numerous papers in order to know the best reaction condition.^[50-53] Among the various DoE methods, the response surface method (RSM) is the most widely used approaches in organic synthesis. RSM is a powerful set of mathematical and statistical techniques based on multivariate statistics, which consist of experimental design, optimization process, and statistical model. This method can offer some advantages that are extremely desirable, such as the absence of solvents, an inexpensive catalyst, and the reaction designed in one pot step in order to limit the synthetic waste, to save time, and to simplify practical aspects through efficiency and environmental sustainability.

Results and discussion

Catalyst characterization

The XRD patterns of nZMOR and nHZMOR catalyst samples are given in Figure 1. The results exhibit that the natural zeolite presence of a major mordenite crystalline phase. Confirmed by XRD pattern, the nZMOR predominantly exhibited peaks at 2θ value 9.62; 13.34; 19.52; 22.14; 23.15; 25.57; 26.39; 27.49, 30.92 and 35.6°, corresponding to the literature and which agreed with the relevant mordenite pattern mentioned in JCPDS File Card (number 80-0645).^[38,54] The XRD patterns between the nZMOR and nHZMOR also showed that the natural zeolite structure was clearly protected through acid treatment. During the treatment, the amorphous material elimination that originally existing in the nZMOR was also observed in the decrement of the amorphous side $(2\theta = 5)$ from nZMOR, which resulted in crystallinity improvement.



Figure 1. The XRD patterns between the nZMOR and nHZMOR.

Table 1. Chemical composition of nZMOR and nHZMOR; all data are expressed for oxides as (%, w/w).

Elements (%)	SiO ₂	Al ₂ O ₃	CaO	Fe ₂ O ₃	K ₂ O	Si/Al ratio
nZMOR	65.45	9.79	9.32	7.36	2.30	6.04
nHZMOR	70.43	9.61	7.21	4.56	1.91	6.61

The elemental composition measurements are given in Table 1. The result shows natural zeolite is predominantly by silica and aluminum and matched as mordenite profile, which is in accordance with a Si/Al ratio intermediate including mordenite and heulandite. As we already know that zeolite consists of [Si(OH)Al] structural unit which is able to play as Brønsted acid, Lewis acids, and/or simultaneously.^[38] During the acid treatment, the number of aluminum atoms are displaced from the NZMOR network, which caused by the dealumination processes and thus followed by the increasing of Si/ Al ratio.^[55]



Figure 2. FTIR spectra of nZMOR (blue) into nHZMOR (black) through ion-exchanged treatment with nZMOR-NH₄⁺ (red).

The FTIR spectra of all the zeolite samples are given in Figure 2. For all samples, the transmittance bands in the range between 600 and $850 \,\mathrm{cm}^{-1}$ and 1050 and 1220 cm^{-1} are connected to the tetrahedral vibrations of internal Si-O (Si) and Si-O (Al) or bridges of silico-oxygen and alumino. There is a small band displacement to higher wavenumbers (Δv =11 cm⁻¹) at 1068 cm⁻¹ for NZMOR compared to nHZMOR, which indicates the elimination of Al3+ ion due to acid treatment by a 6 N HCl solution. The bands in 1630 and 1385 cm⁻¹ are connected to (H-OH) and -(O-H-O) - deformation vibration bands, respectively. The band in the region of $3440 \,\mathrm{cm}^{-1}$ is attributed to the OH group.^[37,56] However, the band at 600 cm^{-1} denotes the double five ring structure of tetrahedral AlO4 and SiO4 units. As can be seen in the FTIR spectra, there is a band at 3637 cm⁻¹ related to acidic hydroxyls Si–O(H)–Al. For nZMOR– NH_4^+ , a band at 1411 cm⁻¹ and at 3168 cm⁻¹ is observed as an ammonium band, which can be connected due to ion exchange with NH₄Cl. nZMOR successfully transformed into nHZMOR, which has a more dominant Brønsted active site by cationic exchange with $nZMOR-NH_4^+$ and its plausible mechanism is proposed in Scheme 1. Calcination treatment at 450 °C leads to the conversion of nZMOR-NH₄⁺ into nHZMOR by releasing NH_3 gas. The significant decrement adsorption bands at 3464 and 1635 cm⁻¹ were represented to the adsorption of -OH stretching and bending of water, respectively. Generally, the results show that the FTIR transmittance patterns of all the samples are identical with respect to the band positions. This could be strong evidence that the acid treatment with 6 N hydrochloric acid over nZMOR does not cause significant structural



Brønsted acid site

Scheme 1. The proposed mechanism of nZMOR treatment into nHZMOR.



Figure 3. SEM images of the parent (NZMOR, left) and dealuminated mordenite (NHZMOR, right) samples.

changes. Through this treatment, it is possible to minimize impurities over nZMOR because of its ability to open the pores wide and work properly as a catalyst which is confirmed by an increase in its surface. The lower amount of water in nHZMOR compared to nZMOR is considered strong evidence that the FTIR analysis (Figure 2) also indicate a decrement of the water amount in nZMOR.

The nZMOR, as well as NHZMOR SEM images, are shown in Figure 3, which emerges in nearly identical morphology. Though, the existence of small size debris and non-uniform were viewed in the nZMOR. However, in the nHZMOR sample relatively neat and unvarying size crystals were seen. This result again reinforces the XRD results representing the acid treatment effect in the nZMOR as the reason for the debris elimination on the nZMOR crystals, producing neat crystal morphology in the nHZMOR catalyst.^[37]

The N₂ adsorption-desorption used further to establish the porous nature of the nZMOR. Based on the adsorption-desorption isotherms of the nHZMOR (Figure 4) there is an increase in the volume of the gas absorbed. The nHZMOR pore size distribution patterns also denote enhancement both in the mesopore and micropore volume pore is ensued. Both nZMOR and nHZMOR consist of three types of pores i.e. R < 2 nm, 2–5 nm and R > 5 nm, which is related to the previous literature.^[57] The complete data given in Table 2 confirms the pore volume properties, micropore area, surface



Figure 4. Nitrogen adsorption-desorption isotherms of nZMOR (blue) and nHZMOR (red).

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Materials	S _{BET} (m ² /g)	S _{BJH} (m²/g)	V _{BJH} (cc/g)	d _{BJH} (nm)	[H ⁺] (mmol/g)
nZMOR	29.294	37.720	0.143	1.926	1.58
nHZMOR	51.456	41.864	0.159	1.8789	0.89

Table 2. Physicochemical properties of the various zeolite samples of the materials studied.

area and external surface area of the acid-treated nZMOR were increased compared to the nZMOR. As shown in Table 2, the treatment using acid on the mordenite enhances the nZMOR characteristics because of dealumination and decationation. In addition, the nZMOR channels are blocked by amorphous silica fragments. However, broader pores are less susceptible to acid treatments. Thus, the mordenite network remains nearly unaffected.

In the TGA result (Figure 5) for the nZMOR and nHZMOR, in the temperature range of 100–200 °C there was little weight loss 14 and 8%, respectively, attributed to the surface dehydroxylation and dehydration at 200–500 °C and the fact that at higher temperatures, isolated hydroxyl groups are easily removed. The main loss of mass is observed due to the desorption of intact water and hydroxyl species at the temperature range between 100and 200 °C and 200 and 400 °C. At T < 100 physically adsorbed water is removed, while hydroxyl groups are eliminated mainly from the surface. Both the TGA and FTIR results are complement with each other from the water loss point of view. These results are also the same as in previous literature.^[38,45,57]

The Brønsted acid site test of nHZMOR was determined by using conductometric titration according to the previous literature.^[55] Conductometric titration of nHZMOR with sodium hydroxide is reasonable method to measure the potential number of Brønsted acid sites. The acidity levels of nZMOR and nHZMOR are 1.48 and



Figure 5. Thermal gravimetric analysis (TGA) of nZMOR (black) and nHZMOR (red).



Scheme 2. nHZMOR-catalyzed Friedel-Craft acylation of the phloroglucinol.

0.89 mmol/g, respectively. The decreasing value of nHZMOR acidity compared with nZMOR is caused by dealumination and dehydroxylation processes during acid treatment.^[55] In addition, XRF analysis (Table 1) showed that the nZMOR Si/Al ratio increased from 6.04 to 6.61, which indicated that acid treatment could reduce the Lewis acid sites from Al and dominantly remained specific Brønsted acid sites.

Selective Friedel–Crafts C-acylation

Effect of temperature and catalyst loading

The synthesis of diacylphloroglucinol condition was carried out to the direct Friedel–Crafts C-acylation from phloroglucinol and acyl chloride or acetic anhydride as the starting material as shown in Scheme 2, and the experimental results are presented in Table 3. Primarily, blank investigate in the nonappearance of a catalyst at room temperature and at 80 $^{\circ}$ C also did not give the desired product after three hours. On the other hand, the presence of nHZMOR can improve the desired product at 80 $^{\circ}$ C. An

Entry	Catalyst	Catalyst loading (% w/w)	Solvent	T (°C)	Time (min)	Yield (%)
1	_	_	Neat	rt	120	-
2	-	_	Neat	50	120	_
3	-	_	Neat	80	120	_
4	nZMOR	10	Neat	rt	120	_
5	nZMOR	10	Neat	80	120	_
6	$nZMOR-NH_4^+$	10	Neat	rt	30	_
7	nZMOR-NH ₄ +	10	Neat	80	30	<40
8	nHZMOR	10	Neat	rt	120	_
10	nHZMOR	3	Neat	80	30	12.8
11	nHZMOR	5	Neat	80	30	40.67
12	nHZMOR	7	Neat	80	30	82.39
13	nHZMOR	10	Neat	80	30	95.35
14	nHZMOR	15	Neat	80	30	90.06
15	nHZMOR	10	CHCl ₃	80	30	94
16	nHZMOR	10	CH ₂ Cl ₂	80	30	89
17	nHZMOR	10	Toluene	80	30	90
18	nHZMOR	10	Ethanol	80	30	<20
19	nHZMOR	10	Aceto- Nitrile	80	30	<20
18	nHZMOR	10	Water	80	30	<10

Table 3. The trial of reaction conditions for the synthesis of diacylphloroglucinol 3c.



Figure 6. Reaction conditions: phloroglucinol (1 mmol), acyl chloride/acetic anhydrides (2 mmol), and nHZMOR catalyst, under neat conditions at 80 °C.

initiation at room temperature also demonstrated but unfortunately did not give the desired product even after three hours. Furthermore, the yield of the reaction did not improve by reaction time addition. Also, the catalyst effect on this reaction was observed. These results showed that the presence of nHZMOR catalyst at 3, 5, 7, and 10% (w/w) (relative to the acylation agent) can increase the yield of diacylphloroglucinol (Figure 6). To our surprise, a lower yield was observed when slightly increasing in the presence of 15% (w/w). Zeolite was found to exhibit bifunctional Brønsted acid and

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Lewis activities that enable phloroglucinol conversion to diacylphloroglucinol. Furthermore, to investigate the reaction was catalyzed by either Lewis or Brønsted acidic sites of nHZMOR, diacylphloroglucinol synthesis was then also carried out in the presence of nZMOR and nZMOR–NH₄⁺. The result was that nHZMOR catalyzed this reaction in a shorter time and with a higher yield compared with the nZMOR and nZMOR–NH₄⁺ catalysts. This result showed clear indications that the Brønsted acid of nHZMOR plays the most important role in this reaction. The Friedel–Crafts acylation reaction could need an extra stoichiometric amount of the Brønsted/Lewis acid based on previous literature.^[25,58] However, the Friedel–Crafts acylation reaction reached an optimum condition of under 10 wt% to above 1 wt% catalyst utilization, which is relating to its nature as a catalyst. From the green chemistry point of view, a lower catalyst loading is preferable to any reaction which needs a large amount of catalyst utilization.

Effect of various solvents

Various solvents such as chloroform, dichloromethane, and toluene, were also used in this reaction and did not increase the product target. The acylation was better in non-polar or weakly polar solvents compared the observed result in polar solvents such as water, ethanol, and acetonitrile. Polar solvent could deactivate catalytic sites and tend to obtained lower yields of product.^[59] Another observed result shows less activities in the presence of various solvent because of competition effect between the substrate molecules and solvent molecules for adsorption on the catalyst. It should be noticed that the acyl chloride or acetic anhydride is a liquid, which thus could act as an acylating agent and solvent in the reaction system. Therefore, the solvent-free reaction condition. The results indicate that the optimized reaction for diacylphloroglucinol synthesis includes 10% (w/w) catalyst, 0.5 h reaction time, and under solvent-free at $80 \,^{\circ}$ C. The pleased yield, short time and easy separation of nHZMOR by simple filtration from the reaction mixture prompted us to explore the possible application of nHZMOR as a catalyst in other numerous diacylphloroglucinol derivatives under optimized conditions.

Design of experimental optimization (DoE)

RSM was applied at this experimental in order to reduce the experimental trials number and later the experiments cost compared to conventional optimization. The experimental variables and the level of their setting are given in Table 4. The prior results and literature report that the temperature and amount of catalyst are vital factors affecting the response (yield) of the Friedel-Craft acylation. A set of 16 experiments was projected for the Friedel-Craft acylation of the phloroglucinol reaction with a two-level factorial and three groups of design points. To observe the presence of curvature in the effects, more experiments were added to the central point of the experimental design. Table 5 shows the experiment designed according to the RSM method, which should be practiced in a laboratory in order to find the reaction yield. Then, this design of experiment was analyzed using the Design Expert software which found a quadratic model which fit for the data and that its coefficients which should possible to calculate the yield of

giaemer and the level of them	,ettig.			
	Level of setting			
Variables	-1	0	1	
X ₁ : reaction temperature (°C)	25	60	80	
X ₂ : Catalyst loading (%w/w)	3	7	10	

Table 4. Experimental variables in the Friedel–Craft acylation of the phloroglucinol and the level of their setting.

Table 5. Experimental design and the yields obtained in the Friedel-Craft acylation of the phloroglucinol using the RSM method.

	I	actors	Perponse
Run	X ₁	X ₂	Yield (%)
1	0	1	15
2	-1	0	10
3	-1	1	10
4	0	0	13
5	0	0	12
6	-1	-1	5
7	0	0	12
8	1	0	66
9	0	1	14
10	0	-1	9
11	0	0	13
12	1	1	92
13	0	-1	7
14	1	-1	33
15	-1	-1	10
16	1	0	54

reaction. Among vital factors i.e. temperature and the amount of catalyst and reliant variables could be defined using a polynomial model as below:

$$Y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \dots + \beta_k x_k + \beta_{12} x_1 x_2 + \beta_{13} x_1 x_3 + \dots + \beta_{k-1,k^{x_{k-1}}} x_k + \beta_{11} x_1^2 + \beta_{22} x_2^2 + \dots + \beta_{kk} x_k^2 + \varepsilon$$
(1)

where $\beta_0, \ldots, \beta_{kk}$ is represented the model coefficient; x and y describe the factors and predicted the reliant variable, respectively. Utilizing a linear optimization technique vector of β can be determined as follow:

$$\beta = (\mathbf{X}^{\mathrm{T}}\mathbf{X})^{-1}\mathbf{X}^{\mathrm{T}}\mathbf{Y}$$
⁽²⁾

The resulted prediction model after optimization and polynomial model is as follow:

$$Y = 12.15605 + 26.60866X_1 + 9.77288X_2 + 13.20425X_1X_2 + 22.76634X_1^2 + -0.56209X_2^2$$
(3)

ANOVA analysis was used to confirm that a quadratic model possibly to envisage the yield of the experimental reaction. As shown in Table 6, the probability model (p-value) was relatively small <0.0001 which showed that the developed model was significant. The X_2^2 probability value was larger than 0.05 (threshold criterion) consequently this expression must be eliminated from the model. The coefficient determination value (R^2) denotes that the model possibly will fit the trial data well and the predicted R^2 also displays that the model possibly to predict the yield of the experimental reaction as

Source	<i>p</i> -Value.>F
Model (yield)	<0.0001
X ₁	<0.0001
X ₂	0.0012
X ₁ X ₂	0.0013
X ₁ ²	<0.0001
X ₂ ²	0.8696
R^2	0.9564
Predicted R ²	0.7896
Lack of fit	0.0093

 Table 6. Analysis of variance (ANOVA) for the response surface quadratic model of the yield.



Figure 7. Contour and 3-D surface plot from the quadratic model (a), displaying the effects of temperature reaction and number of equivalents of catalyst on the Friedel–Craft acylation of the phloroglucinol (b), the prediction vs. actual model. Reaction conditions: phloroglucinol (1 mmol), acyl chloride/acetic anhydrides (2 mmol), and nHZMOR catalyst, under neat conditions at 80 °C.

depicted in Figure 7c. Figure 7a,b shows a surface plot of three-dimensional (3-D), which created permitting to the quadratic model. It proves that the diacylphloroglucinol yield increases rapidly as the reaction temperature rise from 25 to 80 °C and the increase of the catalyst amount from 3 to 10% (% w/w) triggers an increase in the reaction yield. The observed responses and predicted values are shown in Figure 7c. Finally, confirmatory experiments were reached by relating the previous individual study's conclusions. The predicted optimal condition was achieved by the use of maximum temperature and catalyst. Therefore, the actual condition was conducted involving 2 mmol of acetic anhydride as the acylating agent, and 10 (% w/w) catalyst, and performed at 80 °C (Table 7). The obtained yield was 90.2% and this result closely matched with the predicted result of 84% (the error between the actual result and the predicted result was

entry	acylating agent	product	Т	time	yield
		diacylphloroglucinol	(°C)	(min)	(%)
1		но он он он	80	20	76-84
		3a			
2	CI		80	30	88-94
		3b			
3	↓ ⁰ L		80	30	89-95
		3c			

Table 7. Synthesis of diacylphloroglucinol derivatives catalyzed by 10% (% w/w) nHZMOR.

less than 6%). Therefore, the RSM method was found effective for the optimization of the parameters for the synthesis of diacylphloroglucinol.

Effect of various acylating agent

Interestingly, the nHZMOR catalyst was able to catalyze the reaction synthesis of a series of diacylphloroglucinol derivatives bearing different acyl substituents in good yields. The results of the Friedel–Craft C-acylation of phloroglucinol containing various acyl substituents are presented in Table 3. In most studies, the reactions progress smoothly to obtain the corresponding products in reasonable yields within 30–45 min. Accordingly, a reaction under solvent-free conditions was carried out further to analyses and to obtain relevant optimization parameters concerning the reaction conditions through the full factorial DoE method.

Proposed reaction mechanism

The plausible reaction mechanism proposes Friedel-Craft acylation phloroglucinol with nHZMOR catalyst and is presented in Scheme 3 based on the reported literature for Friedel-Craft acylation via its Brønsted active sites. Acylation of an aromatic compound involves the protonation of acylation agent over the introducing of Brønsted active sites of nHZMOR to form an acylium ion intermediate (I). It is generally known that direct Friedel-Craft C-acylation has been successfully informed over strong Brønsted active sites. Since the phloroglucinol nucleus is electron-rich, this reaction is followed by a nucleophilic attack from phloroglucinol as an aromatic system to protonated acylation agent to yield an intermediate (II). Therefore, the nHZMOR catalyzed selective Friedel-Craft C-acylation of phloroglucinol might take place either by direct



Scheme 3. Proposed mechanism of formation diacylphloroglucinol catalyzed by nHZMOR.

Friedel–Craft C-acylation or over the Fries rearrangement reaction of the intermediate O-acyl phloroglucinol, or both mechanisms working at the same time gives monoacyl-phloroglucinol first (III). The remaining electrophilic attacked by another active site from phloroglucinol and with a similar mechanism reaction affords the desired product (IV). An amount of HCl gas is released and leaves the reaction mixture. In all cases, no tri-acyls were formed due to steric hindrance from the bulky group of acyl chloride even in short-chain acylation agents. Converting reactant phloroglucinol with a bulky acyl chloride required a longer time than short-chain acyl chlorides.

Reusability catalyst

These fascinating outcomes regarding the synthesis of diacylphloroglucinol advised us to develop the opportunity of nHZMOR to the various synthesis of diacylphloroglucinol derivatives under enhanced conditions. Amazingly, we were capable to synthesize a series of diacylphloroglucinol containing the different acyl substitutions in high yields. The main advantages of a heterogeneous catalyst system are that it is easy to reuse and is more environmentally friendly. Subsequently, the nHZMOR catalyst was tested for recyclability and reusability in this reaction. The recyclability nHZMOR catalyst in the synthesis of diacylphloroglucinol was tested until the yield decreased significantly. The reaction was done $80 \,^\circ$ C with phloroglucinol: isovaleryl chloride molar ratio of 1:2 using 10% (*w/w*) nHZMOR catalyst for 0.5 h. The results are presented in Table 3.



Figure 8. Recyclability test of nHZMOR in the synthesis of 3c.

Table o. neus	adding test of fiftziv	S 01 3C .			
run	1st	2nd	3rd	4th	5th
Yield (%)	92.86	88.06	86.43	80.64	76.21

Table 8. Reusability test of nHZMOR after regenerated in the synthesis of 3c.

In the final reaction, by simple filtration the nHZMOR catalyst could be easily collected, washing with small amounts of ethyl acetate/acetone and dried at 110 °C for 3 h before being used for further reactions. The results of the reusability test are given in Figure 8. The recyclability experiments gave amazing results, still showing a high quantitative yield even after seven reactions (Figure 8). After following the regeneration treatment by washing with ethyl acetate/acetone and calcination, an increasing trend of diacylphloroglucinol was achieved reaching 41.72% (Table 8). The decreased yield of the product might be attributed to the deactivation phenomenon which happened because the deposed organic compound covered the nHZMOR active sites. Nevertheless, regeneration treatment could increase the last yield conversion of the product target. This indicates that calcination treatment could fully regenerate the catalytic properties of nHZMOR. In practical terms, due to its higher quantitative yield, the recyclability, and the reusability, nHZMOR is suggested as an excellent catalyst for producing diacylphloroglucinol. This method is obviously a simple, high yielding, and environmentally benign phloroglucinol acylation procedure compared with the previous work,^[4,13,15,16] which uses a toxic catalyst and hazardous solvents.

Conclusions

In summary, natural zeolite mordenite was successfully treated via a physical and acid chemical approach as a new heterogeneous catalyst. The treated catalyst was then 16 🛞 W. E. PRASETYO ET AL.

successfully applied for the synthesis of diacylphloroglucinol derivative compounds through the direct Friedel-Crafts C-acylation under solvent-free conditions. The Friedel-Craft acylation reaction was optimized with a statistical strategy using RSM. The optimum conditions achieved by DoE experiments, as follows: (1) the reaction temperature at 80 °C and (2) the catalyst loading at 10% w/w relative to the acylating agents. These experimental and model-predicted values presented an outstanding agreement for nHZMOR as a heterogeneous catalyst for the synthesis of diacylphloroglucinol derivatives. Overall, this approach provides advantages in terms of simplicity, environmental tolerability, excellent yields, and selectivity. It is clearly different from the other methods, which the noticeable features of these eco-benign and environmentally friendly processes included in the preparation of diacylphloroglucinol with a relatively quick procedure and insignificant waste. The catalyst was easy to recover and could be reused several times without a significant loss.

Experimental section

Materials

Natural zeolite (nZMOR) was collected from Wonosari, Yogyakarta, Indonesia. All reagents were used devoid of further purification. Phloroglucinol, acetic anhydride, isobutyryl chloride, isovaleryl chloride, hydrochloric acid, ammonium chloride, acetone, ethyl acetate, chloroform, dichloromethane, toluene, sodium hydroxide and silica gel for column were supplied from Sigma-Aldrich Co. Thin layer chromatography Silica gel 60 G F_{254} 25 Glass plates were purchased form E-Merck. Before further used, all of the laboratory glassware was cleaned with *aqua regia* and rinsed with deionized water.

Instrumentation

XRD measurements were used on a Shimadzu Lab-X 6000 diffractometer with Cu K α radiation ($\lambda = 1.5418$ Å) in the range of $0^{\circ} \le 2\theta \le 40^{\circ}$. X-ray fluorescence (XRF) was recorded by X-ray fluorescence ED XRF S2 Ranger Bruker Cu K Alpha Radiation. To Barrett-Joyner-Halenda measure the (BJH) specific surface area, Brunauer-Emmett-Teller (BET) specific surface area, specific pore volume, pore volume distributions of small macropores and mesopores, an Autosorb-iQ (Quantachrome Co., USA) was used employing liquid N₂ at 77.3 K. Infrared spectroscopy was performed on FT-IR, Prestige 8201 PC, with Potassium Bromide (KBr) Pellet over the $4000-400 \text{ cm}^{-1}$ region at room temperature. The SEM images were recorded on JEOL JSM-7900F instrument Japan. The ¹H NMR experiments were recorded on an AGILENT VNMR (500 MHz) spectrometer. The chemical shifts were reported in parts per million (ppm). Coupling constant (J) reported in Hertz (Hz). The thin-layer chromatography was performed with TLC Silica gel 60 G F_{254} and visualized by exposure to UV Light (254 nm). Melting points in °C were determined in open capillaries using Melting Point Apparatus SMP10 Stuart.

Thermal treatment and acid treatment of nZMOR

nZMOR was stirred with deionized water with ratio solid to volume 1:3 (g/mL) for 2 hours. The unwanted materials were removed by filtering and the resulted slurry was dried for 3 hours at 105 °C. It was treated by dealumination treatment with HCl and cationic exchanged with NH₄Cl. nZMOR was heated in HCl 6 N solution at 50 °C and then dried perfectly in an oven at 90 °C. An hour later, it was heated in 100 mL NH₄Cl solution at 50 °C for 7 days to obtain nZMOR-NH₄⁺. Thermal deammonification was carried out at 450 °C for 6 h for converting nZMOR-NH₄⁺ to nHZMOR.

Synthesis of diacylphloroglucinol derivatives over nHZMOR catalyst

To a mixture of phloroglucinol (1 mmol), acyl chloride/acetic anhydride (2 mmol), and nHZMOR were added in 100 mL three-neck round bottom flask. The mixture was mixed uniformly for 15 minutes at room temperature. Then, the resulted mixture heated at 80 °C under an inert atmosphere until most of phloroglucinol was consumed and monitored by TLC. After completing reaction, the mixture cooled down to room temperature and aquades (15 mL) and EtOAc (25 mL) were poured. The mixture filtered to separate between the organic phase and catalyst. The resulting mixture was extracted, then the organic phase separated, then the aqueous phase was well extracted with EtOAc (3×25 mL) and with saturated NaCl (1×10 mL). The organic layer was added with Na₂SO₄ and concentrated under *vacuo*. The obtained crude product was purified by column chromatography (silica gel, eluted with n-hexane: EtOAc 7:3 and 6:4) to afford pure diacylphloroglucinol. The catalyst recovery was done by filtration and washing with EtOAc & acetone (20 mL), then dried at 120 °C for 3 h before reused for further reaction. The obtained products were analyzed by ¹H NMR, FTIR, and their melting points.

Design of experiments (DoE)

Design of experiments used to observe the quantitative effect of the operating conditions (parameters) against the product conversion (response) of the Friedel–Craft acylation reaction of phloroglucinol with acylating agents using an nHZMOR. It can obtain useful information for future economic optimization of the global process.^[53] The DoE experiment was performed with Design Expert software 10.

Recyclability and reusability test of the catalyst

After nHZMOR used in this reaction, it was recovered by filtration and washed with ethyl acetate (20 mL) and acetone (20 mL), then dried at 80 $^{\circ}$ C after each run before reused for further reaction. For reusability test, initially, similar treatment was applied like recyclability test procedure. Further step was followed by calcination for 6h at 450 $^{\circ}$ C to remove the organic template before the next reactions.

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ORCID

Triana Kusumaningsih (b) http://orcid.org/0000-0002-5795-0125 Maulidan Firdaus (b) http://orcid.org/0000-0001-8813-3649

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