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GREEN SYNTHESIS OF SEVERAL CHALCONE DERIVATIVES USING GRINDING TECHNIQUE

Susy Yunita Prabawati[1*], Kurniawan Eka Yuda[1], Rizki Cahya Firdaus[1], Agianti Sugihati[1]

Chemistry Departement, Faculty of Science and Technology, UIN Sunan Kalijaga Yogyakarta Indonesia[1]

Corresponding author: 1*

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4-dimethylamino-4-hydroxy chalcone (DMAHC), 4-dimethylaminobenzalacetone (DMAB), 6-fluoro-2-chloro-4-hydroxychalcone (FCHC), Claisen-Schmidt condensation, grinding.

ABSTRACT

Chalcone and its derivatives are known for their biological activities such as antibacterial, anticancer, antioxidant, and anti-inflammatory. This research conducted a synthesis of chalcone derivatives, namely 4-dimethylamino-4-hydroxy chalcone (DMAHC), 4-dimethylamino benzal acetone (DMAB), and 6-fluoro-2-chloro-4-hydroxy chalcone (FCHC) by grinding technique. The grinding technique was successfully carried out with zero solvents to minimize waste production. Claisen-Schmidt condensation reaction with NaOH as a base catalyst was employed in this study to synthesize chalcone compounds. The grinding process was succesfully applied in a very short time, approximately 15 minutes. The derivative products, DMAHC, DMAB, and FCHC, were produced in the form of yellow solids with melting points of 67, 65, and 189°C with yields of 46.32, 33.49, and 26.55%, respectively. FTIR spectrophotometer characterized a sharp absorption in around 1660 cm^{-1} as a typical absorption of the C=O carbonyl functional group of chalcone derivatives. The analysis results with ^{1}H-NMR showed the appearance of proton absorption in the chemical shift (δ) between 7.6 and 7.8 ppm as the proton absorption of the alkene group (-CH=CH-) from chalcone derivatives.

1. INTRODUCTION

Chalcone and its derivatives are secondary metabolites of the flavonoid group commonly found in many plants. However, chalcones usually have low amounts in plants with relatively limited structural variations. Therefore, as desired, the synthesis pathway attempts to obtain chalcone compounds and their derivatives with greater yields and structural variations [1].

From its structure, chalcone provides a reactive ethylene keto group (-CO-CH=CH-). The presence of these groups causes chalcone to have various biological and pharmacological activities such as anticancer [2- 4], cytotoxic [5], antimicrobial [6], antimalarial [7], antibacterial [8- 10], and anti-leismanial [11].

Chalcone-derived compounds can be synthesized through a cross-aldol condensation reaction or Claisen-Schmidt condensation involving an aromatic aldehyde with a ketone [12] under acidic or basic conditions followed by a dehydration reaction. Acid catalysts commonly used is HCl and $SOCl_2$, while NaOH

commonly used as the base catalyst [13].

Generally, the synthesis of chalcone-derived compounds is carried out by conventional methods, namely by reflux, which requires a large amount of solvent and a long reaction time. Grinding as a solvent-free method has begun to be widely used as an alternative method. This technique grids the material in a mortar without using solvents or heating [14]. The product of the reaction depends on the process of crushing the material [15].

Several previous studies have also used grinding techniques in the synthesis of a compound with satisfactory results [16], [17]. The grinding technique also provides other advantages, such as more products obtained [18], a shorter reaction time at room temperature [19], and more greenness because less solvent is needed so it minimize the waste production [15]. Based on the backgroud, this study aims to synthesize chalcone derivatives, namely DMAHC, DMAB, and FCHC by grinding technique with a NaOH base catalyst.

2. EXPERIMENTAL SECTION

2.1 Chemicals

The chemicals used in this study were 4-dimethylamino benzaldehyde (Merck), 4-hydroxy-acetophenone (Merck), acetone, 6-fluoro-2-chlorobenzaldehyde (Sigma Aldrich), Sodium Hydroxide (NaOH), ethanol, hydrochloric acid (HCl), chloroform and distilled water.

2.2 Apparatus

This study employed a set of laboratory glassware, analytical balance (OHAUS), hot plate (CIMAREX), filter paper, mortar, grinder, melting point apparatus, oven, Buchner filter, FTIR spectrophotometer (Shimadzu FTIR-8201 PC) and 1H-NMR spectrophotometer (JEOL JNM) ECA500).

2.3 Procedure

2.3.1 Synthesis of 4-dimethylamino-4-hydroxy chalcone (DMAHC)

5 mmol of 4-hydroxy acetophenone and 40 mmol of NaOH were crushed in a mortar for 10 minutes, then added 5 mmol of 4-dimethylamino benzaldehyde and crushed again for approximately 15 minutes. The paste was left and then dissolved in 10 mL of ethanol, stirred for 1 hour, and stored at room temperature for 24 hours. The mixture was diluted with cold water and acidified with 0.1 M HCl. The reaction mixture was then extracted with 10 mL of chloroform. After the organic layer was taken, the product obtained was measured its melting point and characterized using FTIR and ^{1}H-NMR spectrophotometers.

2.3.2 Synthesis of 4-dimethylaminobenzalacetone (DMAB)

5 mmol 4-dimethylamino-benzaldehyde and 10 mmol NaOH were together crushed in a mortar for 10 minutes. Then, 40 mmol of acetone was added into the mortar and crushed again for 15 minutes. The paste was left for 1 hour and then added with 15 mL of cold distilled water. The mixture was stored for 24 hours at room temperature. The following procedure applied was same as that for DMAHC synthesis.

2.3.3 Synthesis of 6-Fluoro-2-Chloro-4-Hydroxy Chalcone (FCHC)

2.5 mmol of 4-hydroxy-acetophenone and 10 mmol of NaOH were chrused in a mortar for around15 minutes. Then, 2.5 mmol of 6-fluoro-2-chlorobenzaldehyde was added and chrused for approximately 20 minutes until a paste was formed. After an hour, the obtained paste was dissolved in 10 mL of ethanol and stirred for an hour. The solution was stored at room temperature for 24 hours. The following procedure

applied was same as that for DMAHC synthesis.

3. RESULT AND DISCUSSION

The chalcone derivatives, DMAHC, DMAB, and FCHC, had been successfully synthesized through the Claisen-Schmidt condensation reaction. The grinding technique was executed by grinding the material in a mortal for 15 minutes without using any solvent. The reaction product was a yellow solid with a yield of 46.32; 33.49 and 26.55%, respectively.

The reaction was initiated with the formation of enolate ions due to the release of alpha hydrogen (Hα) by the NaOH catalyst. The enolate ion then acts as a nucleophile attacking the aldehyde's carbonyl group and producing β-hydroxy ketone compounds. The mechanism of the Claisen-Schmidt condensation reaction in this study is shown in Figure 1.

The product of this condensation reaction is straightforward to dehydrate. The release of H_2O caused the formation of a double bond at positions α, β to form chalcone derivatives. The detail the dehydration reaction is in Figure 2.

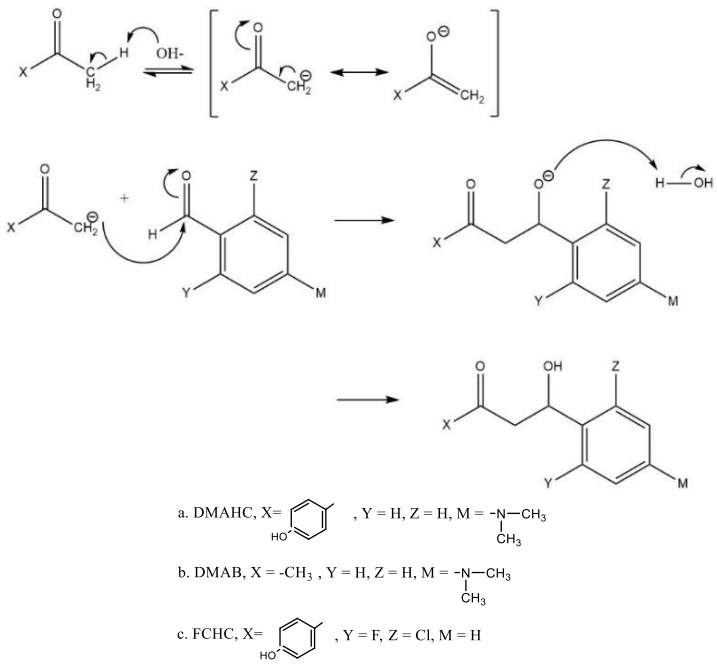

Figure 1. Mechanism of Chalcone Derivative Compounds Formation

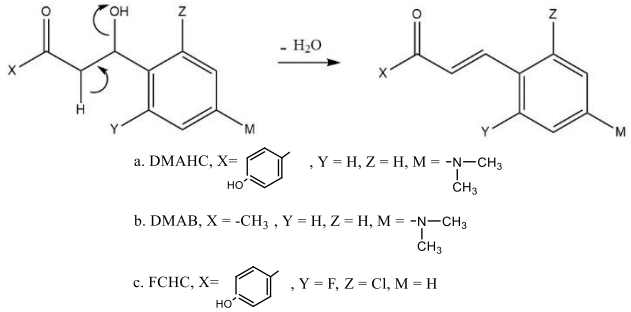

Figure 2. Dehydration Mechanism in Formation of Chalcone Derivative Compounds

Figures 3, 4, and 5 show the FTIR spectrophotometer identification of DMAHC, DMAB, and FCHC,

respectively. The FTIR spectra show a strong absorption in the area around 1660 cm^{-1}, typical of the C=O carbonyl functional group. It can be seen that there was a change in the absorption peak of the C=O carbonyl group from a wave number of about 1700 cm^{-1} to around 1660 cm^{-1} in the chalcone derivative product. This shifting was because of weaker C=O bond in the chalcone derivative than the C=O bond in the base material. [13] confirms the characteristics of the C=O group of chalcone-derived compounds appeared between 1630 and 1660 cm^{-1}.

The absorption in the 3093.82 cm^{-1} shows aromatic C-H range and 2916.21 cm^{-1} for aliphatic C-H absorption. The adsorption in the area of 3055.24 cm^{-1} indicates the presence of alkene C-H absorption. The adsorption of C=C in the area of 1604.77 cm^{-1} is supported by overtone absorption in the area of 1897.95 cm^{-1}.

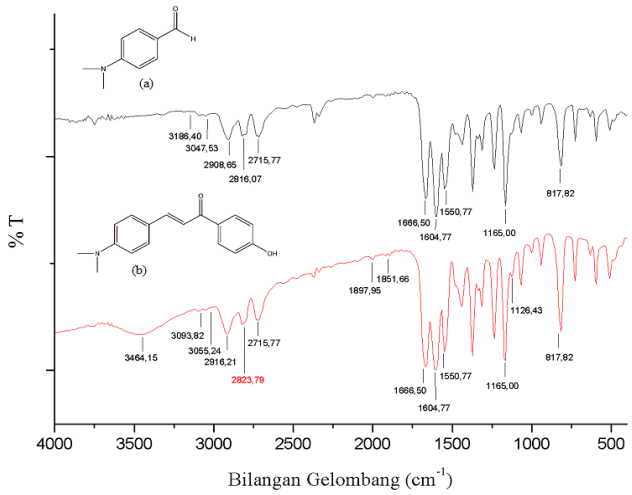

Figure 3. FTIR Spectrum of DMAHC Compound

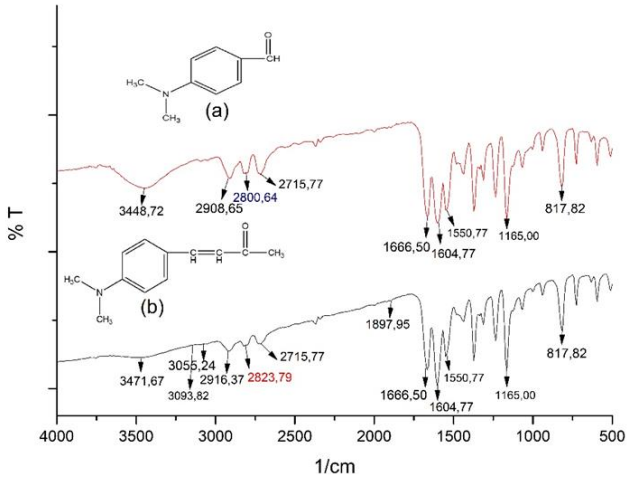

Figure 4. FTIR Spectrum of DMAB Compounds

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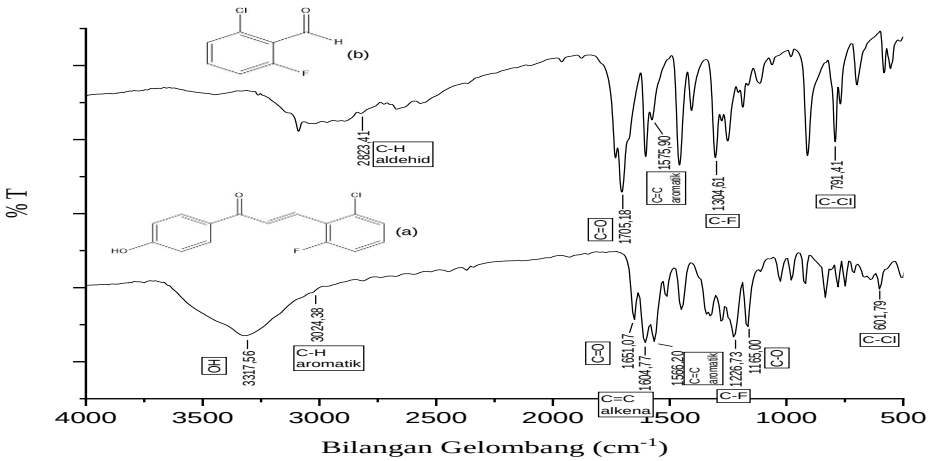

Figure 5. FTIR Spectrum of FCHC Compounds

The loss of absorption peak at wave number 2800 cm^{-1} which is the character of the C-H group of aldehydes is an indication that strengthens the formation of chalcone derivatives. It is supported by absorption in the 2823.79 cm^{-1} as the indication of the C-C group vibrations on the ketones.

The ^{1}H-NMR spectrum of DMAHC, DMAB, and FCHC areshown in Figures 6, 7 and 8, respectively. The proton absorption shows the absorption characteristics of chalcone-derived compounds in the chemical shift (δ) between 7.6-7.8 ppm which is the proton absorption of the alkene group (-CH=CH-). The protons in the (-CH=CH-) group of alkenes that are directly bonded to the carbonyl group have a shift away from TMS by comparing to (-CH=CH-) aromatics. It is because the group (-CH=CH-) attached to C=O is affected by the induction effect of the O atom, so the protons are less protected.

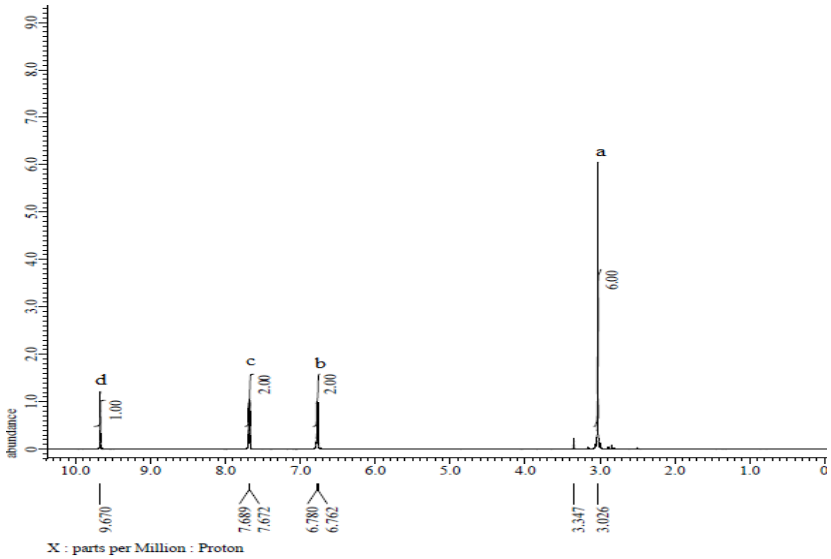

Figure 6. ^{1}H-NMR Spectrum of DMAHC

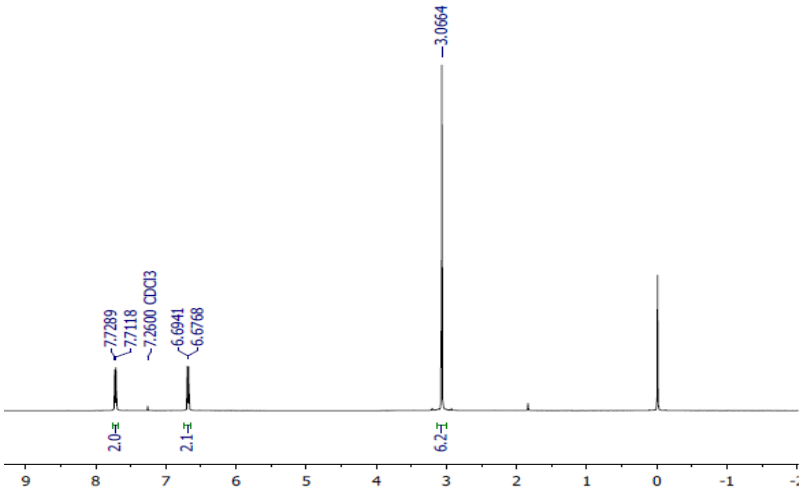

Figure 7. [1]H-NMR Spectrum of DMAB

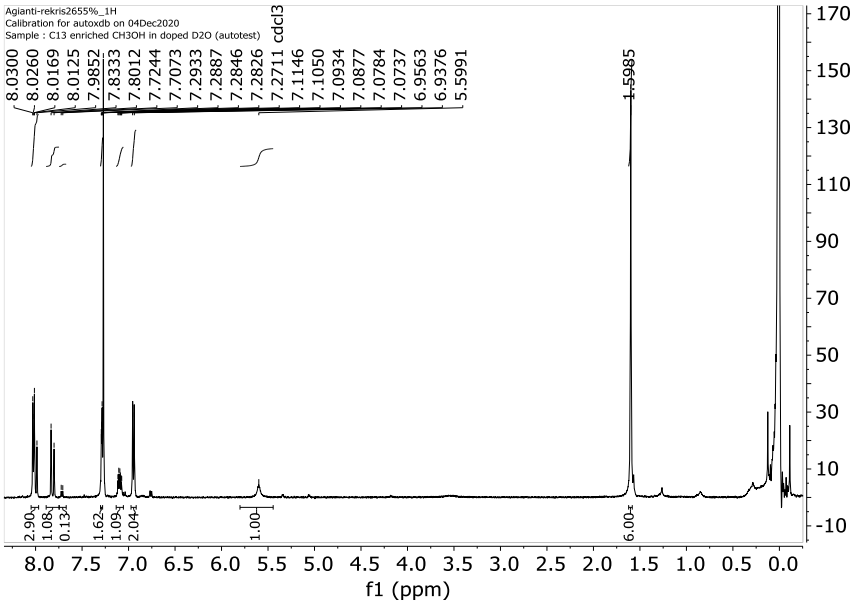

Figure 8. [1]H-NMR Spectrum of FCHC

The grinding technique to synthesis chalcone-derived compounds performed good results. Compared to reflux process as previous result by [10] in synthesizing (E)-2'-hydroxy-2-bromo-4,5-dimethoxychalcone, this study is more effective. The Claisen-Schmidt condensation reaction with the reflux process required a reaction time of 24 hours. However, the grinding technique in this study needed much shorther time, about 1.5 hours, and less solvent used.

The presence of active groups in chalcone derivatives, namely unsaturated α, β ketone groups (-CO-CH=CH-) makes these chalcone derivatives have various biological and pharmacological activities. In addition, the activity of chalcone-derived compounds also depends on the type of substituent attached to the two aromatic rings [20]. Therefore, the development of synthesis of chalcone-derived compounds with various types of functional group variations still needs to do. Synthesizing chalcone derivatives by grinding technique become a potential method to develop because of its ease and fast reaction process.

4. CONCLUSION

Chalcone derivatives, namely DMAHC, DMAB, and FCHC, had been successfully carried out through the Claisen-Schmidt condensation reaction using grinding technique. A very short reaction time was required to synthesize the chalcone-derived compounds, only about 1.5 hours. The reaction product is a yellow solid with melting points of 67, 65 and 189 °C with a yield of 46.32; 33.49 and 26.55%, respectively.

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