

# Green Synthesis of 4-Hydroxy-4'-Methoxychalcone by Grinding Techniques

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**Abstract:** The synthesis of the 4-hydroxy-4'-methoxychalcone has been synthesized by grinding techniques. This compound was synthesized by reacting 4-hydroxybenzaldehyde with 4-methoxy acetophenone using NaOH catalyst in a mortar for 30 minutes at room temperature. The reaction product was monitored by TLC and then recrystallized from ethanol, and golden yellow crystals were obtained. Characterization of synthesized compounds with <sup>1</sup>H-NMR and <sup>13</sup>C-NMR. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, δ ppm): 3,86 (3H, s, H-OCH<sub>3</sub>), 6,86 (2H, d, J=10, Ar-H), 7,07 (2H, d, J=5 Hz, Ar'-H), 7,66 (1H, d, J=15, H-Cα), 7,75 (1H, d, J=7, H-Cβ), 7,73 (2H, d, Ar-H), 8,14 (2H, d, J=9 Hz, Ar'-H), 10,09 (1H, s, UH-OH). <sup>13</sup>CNMR (CDCl<sub>3</sub>, δ, ppm): 187,28 (C=O), 163,04 (C4'), 160,01 (C4), 143,70 (C=C-β), 130,95 (C2' dan C6'), 130,82 (C2 dan C6), 130,77 (C1'), 125,98 (C1), 118,44 (C=C-α), 115,84 (C3 dan C5), 113,99 (C3' dan C5'), 55,57 (-OCH<sub>3</sub>). The results of <sup>1</sup>H-NMR and <sup>13</sup>C-NMR characterization showed that the synthesized compound had been formed.

## 1 INTRODUCTION

Chalcone (1,3-diphenyl propenone) is an intermediate agent in synthesising various heterocyclic compounds (Patil, et al., 2009). Chalcone can be synthesized using Claisen-Schmidt condensation, a condensation reaction between aromatic aldehydes and aromatic ketones to form α, β-unsaturated ketones. Claisen-Schmidt condensation can occur in an acid or base. The use of acid catalysts in condensation reactions (e.g., HCl, BF<sub>3</sub>, B<sub>2</sub>O<sub>3</sub>) generally gives low yields (10-40%) (Patil, et al., 2009). The KOH catalyst in the synthesis reaction of chalcone through the Claisen-Schmidt reaction obtained an 88-94% yield (Zangade, et al., 2011). The use of Ba(OH)<sub>2</sub> in the synthesis of chalcone derivatives was obtained with a yield of 88-98% (Rateb, Zohdi, 2009), and the NaOH catalyst obtained a yield of 90-96% (Mogilaiah, et al., 2010). The Claisen-Schmidt reaction in the synthesis of chalcone with NaOH catalyst gave better results (yield 93-98%) than using KOH, NaOAc, and NH<sub>4</sub>OAc (yield 81-85%) (Rahman, et al., 2012). Moreover, the Claisen-Schmidt reaction is essential in synthetic organic chemistry. The synthesis of chalcone through the Claisen-Schmidt condensation reaction has been widely used (Prasad, et al., 2008).

Susanti (Susanti, et al., 2012 and 2014) have synthesized hydroxy chalcone from hydroxy acetophenone and methoxy benzaldehyde through conventional Claisen-Schmidt condensation using ethanol solvent. Their results revealed that the formation of hydroxy chalcone compounds requires a strong base (50%), a long reaction time (24 hours), and a low yield (40-70%). Thus, this current research will develop a new chalcone synthesis design through the green chemistry approach, namely solvent-free synthesis using grinding techniques (Susanti, et al., 2014).

The grinding technique in synthesis is the development of chalcone synthesis, which is very profitable because it uses very simple equipment, namely pestle and mortar. Chalcone synthesis was modified using grinding techniques to synthesize chalcone compounds from 2-acetyl-1-naphthol and benzaldehyde (Zangade, et al., 2011). Meanwhile, synthesized chalcone with this technique running without solvent, short reaction time (4-8 minutes), and high yields (84-95%). Grinding techniques have also been used to synthesize chalcone from cyclohexanone and benzaldehyde, giving 96-98% yield. Susanti have also synthesized three derivatives of hydroxy chalcone compounds using this technique and yielded 70-84% (Susanti, et al., 2014). However, this grinding technique has not been performed to

synthesize the chalcone derivative of 4-methoxyacetophenone with substituted benzaldehyde. In this study, a new chalcone derivative of 4-methoxyacetophenone and 4-hydroxybenzaldehyde will be synthesized.

## 2 RESEARCH METHODS

### 2.1 Materials

The materials used in this study had analytical grade quality from E-Merck, including 4-hydroxybenzaldehyde, 4-methoxyacetophenone, sodium hydroxide, hydrochloric acid, sulfuric acid, acetone, ethyl acetate, ethanol, n-hexane, chloroform, methanol, dichloromethane, and anhydrous sodium sulfate.

### 2.2 Instrumentation

Instruments in this study were laboratory glassware, analytical scales (Libror EB330 Shimadzu), magnetic stirrer, chromatography column, reflux device, desiccator, magnetic stirring plate, Buchi evaporator, 254 nm UV lamp, Whatman paper no 1, test tube, callipers, magnetic resonance spectrometer Proton core (1H-NMR, 500 Mhz) and carbon (13C-NMR, 125 MHz), and JEOL-MY500.

### 2.3 Procedure

The chalcone compound was synthesized by grinding 4-methoxyacetophenone with 4-bromobenzaldehyde in a mortar and pestle at room temperature for several minutes. The completeness of the reaction was monitored by Thin Layer Chromatography (TLC). The reaction mixture was then diluted with cold water, neutralized with a cold solution of HCl 10% (v/v), then filtered. Purification was carried out by employing recrystallization. The synthetic products were then characterized using <sup>1</sup>H- and <sup>13</sup>C-NMR spectrometers.

## 3 RESULTS AND DISCUSSION

### 3.1 Synthesis of Chalcone by Grinding Techniques

The synthesis of chalcone compounds using grinding techniques was carried out by grinding 4-methoxyacetophenone, 4-hydroxybenzaldehyde, and

solid NaOH in mortar. This grinding process was performed at room temperature for 30 minutes. In this process, friction energy was generated from local heat due to collisions between reactants, which accelerate the reaction to form products. The monitoring of the results of the synthesized compounds was conducted using Thin Layer Chromatography. The synthesis results in yellow crystals as much as 0.8 g (32.5% yield) were obtained after the recrystallization process using ethanol. Characterization of chalcone compounds was done using a <sup>1</sup>H-NMR spectrometer. The <sup>1</sup>H-NMR spectrum of the NMR chalcone compounds, as presented in Figure 1, showed 14 protons in the synthesized compound. The absorption peak at the chemical shift ( $\delta$ ) of 3.85 ppm was thought to be a proton signal from the methoxy group with a singlet and 3-integrated appearance. The singlet appearance indicates that no neighboring protons were coupling these protons. The absorption at 6.84 ppm chemical shift with a doublet's appearance was a signal from the protons from C3 and C5 in the aromatic ring B. This doublet appearance occurred because the protons in C3 and C5 were one neighbouring proton.

The chemical shift at 7.06 ppm was the proton signal owned by C3' and C5' (aromatic ring A). This assumption was strengthened because the peak at 7.06 ppm had a doublet appearance, revealing that the protons C3' and C5' had the same environment, one neighbouring proton. A peak with a similar appearance also occurred at the chemical shift of 7.73 ppm (the protons in C2 and C6) and 8.14 ppm (the protons in C2' and C6'). Olefin protons of  $\alpha$ ,  $\beta$ -ketone unsaturated were observed at the chemical shift of 7.64 and 7.75 ppm with coupling constants  $J = 9$  and  $15$  Hz, respectively. It revealed that the chalcone formed had a trans structure. The peak at 10.09 ppm has a singlet appearance which is the unprotected absorption of hydroxy protons due to the induction of the electronegative O atom. The results of chalcone <sup>1</sup>H-NMR spectral analysis are presented in Table 1.

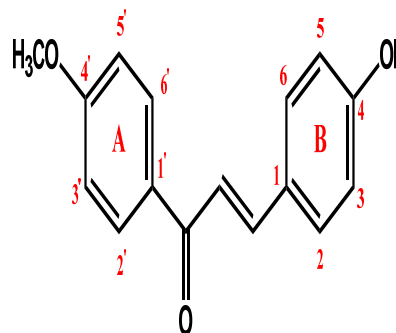
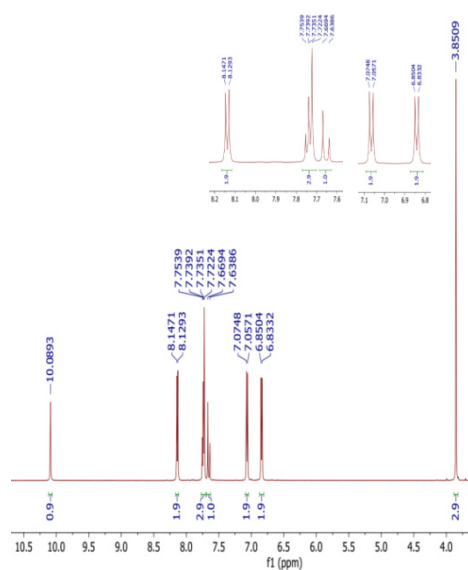
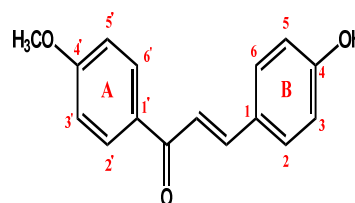
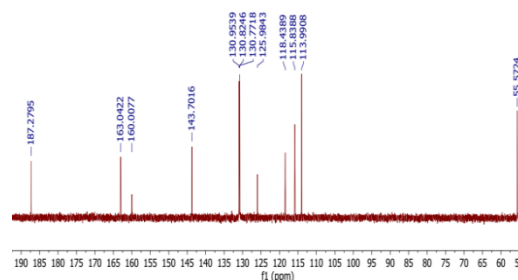


Figure 1a. <sup>1</sup>H -NMR spectrum of chalcone

Figure 1b.  $^1\text{H}$ -NMR spectrum of chalconeTable 1. Results of the  $^1\text{H}$ -NMR spectral analysis of chalcone 1

Chemical Shift $\delta$ (ppm)	Appearance	Coupling Constants $J$ (Hz)	Number and Type of Proton
3,86	singlet		3H, $-\text{OCH}_3$
6,84	doublet	10	2H at C3 & C5
7,07	doublet	5	2H at C3' & C5'
7,66	doublet	15	1H at C- $\alpha$
7,73	doublet	7,5	2H at C2 & C6
7,75	doublet	7	1H at C- $\beta$
8,14	doublet	9	2H at C2' & C6'
10,09	singlet		1H at OH

The structural characterization of the synthesized compounds was further strengthened by the  $^{13}\text{C}$ -NMR analysis (Figure 2), which exhibited 12 signals and indicated the presence of 12 different carbons. The absorption for methoxy carbon was observed at a chemical shift of 55.65 ppm. The carbonyl band ( $\text{C}=\text{O}$ ) was shown at a far chemical shift (deshielding area), at chemical shift 187.28 ppm. It is following Mostahar who asserted that the carbonyl carbon from chalcone usually appears in the area of 170-194.6 ppm (Mostahar et al., 2007). The carbon is bonded directly to the O atom, which has a large electronegativity so that the electrons around the C atom increasingly unprotect the nucleus of the C atom due to being attracted by the O atom.

Figure 2a.  $^{13}\text{C}$ -NMR Spectrum of chalconeFigure 2b.  $^{13}\text{C}$ -NMR Spectrum of chalcone

Carbon with the same environment will appear as one peak in the 113.9 ppm chemical shift, which is the absorption of C3' dan C5'. The same thing happened to absorption at 115.8 ppm (C3 and C5), 130.8 ppm (C2 and C6), and 114.09 (C2' and C6'). The absorption of C $\alpha$  was observed at a chemical shift of 119.4 ppm, while C $\beta$  was at 143.7 ppm. The C- $\beta$  peak appeared more downfield than the C- $\alpha$  atom. It is aligned with Mostahar et al. research (2007), which uncovered that the C- $\beta$  absorption of chalcone compounds appeared in a more remarkable chemical shift than C- $\alpha$ . In detail, the results of the chalcone  $^{13}\text{C}$ -NMR spectral analysis are presented in Table 2.

Table 2. Results of the  $^{13}\text{C}$ -NMR spectral analysis of chalcone

Chemical Shift $\delta$ (ppm)	Type of Carbon
187,28	C=O
163,04	C4'
160,01	C4
143,70	C- $\beta$
130,95	C2' dan C6'
130,82	C2 dan C6
130,77	C1'
125,98	C1
118,44	C- $\alpha$
115,84	C3 dan C5
113,99	C3' dan C5'
55,57	C-OCH $_3$

Based on the  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR analysis results that have been carried out, it could be stated that chalcone, namely 4-hydroxy-4'-methoxychalcone, has been formed from the results of the Claisen-Schmidt condensation process between 4-methoxyacetophenone and 4-hydroxybenzaldehyde. The synthesized product was a yellow crystal. The chalcone formation reaction was assumed to follow the condensation aldol reaction mechanism. The reaction started from an acid-base reaction, where the base took a proton from the  $\alpha$  carbon of 4-methoxyacetophenone to form an enolate ion, which stabilized by resonance. The nucleophilic addition of carbanions from 4-methoxyacetophenone then occurred to the carbonyl carbon of 4-bromobenzaldehyde, followed by releasing water molecules with acids' help form double bonds (Figure 3).

Synthesis of chalcone using grinding techniques is a strategic breakthrough because it considers the principle of green chemistry, namely reducing the use of solvents in the synthesis process. Solvents in the synthesis of many compounds are toxic and cause environmental problems. Therefore, it is vital to develop a method of compound synthesis without a solvent. In the grinding process, all reactants are crushed in a mortar. The collision between the reactants occurs and creates friction energy from local heat, accelerating the reaction to form chalcones.

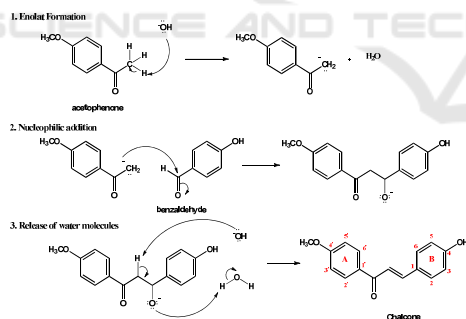


Figure 3. Reaction Mechanism in Chalcone Synthesis

## 4 CONCLUSION

The development of environmentally friendly synthesis methods needs to be developed continuously. The use of grinding techniques in chalcone synthesis is a route with great potential to be developed. Researchers have successfully synthesised 4-hydroxy-4'-methoxy-chalcone by reacting 4-methoxyacetophenone and 4-hydroxybenzaldehyde through a green chemistry approach with grinding

techniques. The study of this compound application as an active antibacterial compound is ongoing.

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