Synthesis and Characterization of Some Bromochalcones Derivatives

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Abstract. Chalcones are considered to be precursors of flavonoids and have variety of biological activities. Three of bromochalcones derivatives were synthesized by a green chemistry approach using grinding technique and their structure also confirmed. Synthesis of bromochalcone, 4′-bromo-4-methoxychalcone, 4′-bromo-3,4-dimethoxychalcone, 4′-bromo-3,4,5-trimethoxychalcone were carried out using starting material of 4-bromoacetophenone through Claisen-Schmidt base catalyzed condensation. The structures of the synthesized compounds were confirmed by gas chromatography–mass spectrometry (GC-MS). The mass spectra of the compounds were showed corresponding molecular ion peak which was correlated with their molecular weight of that respected compound (4′-bromo-4-methoxychalcone = 317, 4′-bromo-3,4-dimethoxychalcone = 347, 4′-bromo-3,4,5-trimethoxychalcone = 377).

1. Introduction
Chalcone is a class of flavonoids, which are intermediates in flavonoid biosynthesis, so the role of these compounds is very important because it is an intermediate in the synthesis of other flavonoid derivatives [1]. Chalcone is found in various plant families but its numbers are very limited compared to other flavonoids because this compound is a minor category of flavonoids so that the percentage in small plants and the variation of its structure is relatively small [2]. Isolation of chalcone from plants is very difficult because of the enzyme chalcone synthetase (CSH) which will convert chalcone into flavones, so the isolation of chalcone from plants requires a relatively long time and is relatively expensive, so to get chalcone in various structures and a large amount can be done by synthesis [3].

Chalcone synthesis can be carried out through aldol condensation or more specifically the Claisen Schmidt condensation reaction, which is a condensation reaction of an aromatic aldehyde with an aromatic ketone in an acidic or alkaline atmosphere. This condensation is widely used in the reaction of the formation of carbon-carbon bonds because the reaction is simple, the raw material is easy to obtain, environmentally friendly and the reaction time is relatively not too long [3]. Chalcone compounds can be synthesized from acetophenone reacted with 3,4-dimethoxybenzaldehyde through Claisen-Schmidt condensation [3]. Claisen-Schmidt condensation reaction alkaline analysis will not form a mixture, because substituted benzaldehyde does not have H-α, so it does not form enolate. Benzophenone derivatives can form enolates and react with aldehydes faster than with themselves, because the aldehydes are more electrophilic than ketones [1]. The most widely used base catalyst is NaOH because of the greater yield [4]. Some base catalysts that have been used in the Claisen-Schmidt reaction are KOH (yield 88-94%) [5], Ba(OH)2 (yield 88-98%) [6], NaOH (yield 90-96%) [7].

Schmidt Claisen can be carried out in two ways, conventional (with solvent) and grinding techniques (without solvents). Susanti (2014) stated that the use of solvents in condensation reactions in the synthesis of chalcone derivatives is hazardous to health and not environmentally friendly, so that a green chemistry approach is needed [8]. Green chemistry is a new method to reduce chemical...
hazards besides producing products in a more efficient and more efficient way. Grinding technique is a synthesis technique without using solvents, this technique is done by grinding all the reactants in a mortar so that the collisions between reactants occur and cause frictional energy from local heat which will accelerate the formation of chalcone [8]. In the previous study, hydroxy chalcone was synthesized from hydroxy acetophenone and benzaldehyde through Claisen-Schmidt condensation using conventional ethanol solvents. The results showed that the formation of hydroxy chalcone compounds required strong bases (50%), long reaction times (24 hours) and low yields (40-70%) [3,8], so that this study will be developed. The new design of synthesis of 3 bromo chalcone compounds from acetophenone substituted with bromo and methoxy substituted benzaldehyde (4-methoxybenzaldehyde, 3,4-dimethoxybenzaldehyde and 3,4,5-trimethoxybenzaldehyde) through a green chemistry approach of solvent-free synthesis using grinding techniques.

2. Experimental

2.1 Materials

4-bromoacetophenone, 4-methoxybenzaldehyde, 3,4-dimethoxybenzaldehyde, 3,4,5-trimethoxybenzaldehyde, sodium hydroxide, HCl, anhydrous Na₂SO₄, silica gel 60-F254, iodine, ethanol, ether, EtOAc, CDCl₃, n-hexane, acetone. General chemicals were purchased from Merck or Aldrich, and were used without further purification. All solvents (Merck) were used without further purification.

2.2 Procedure

The bromo chalcone were synthesized as mentioned in the reference [8]. A mixture of 4-bromoacetophenones (10 mmol), benzaldehyde (10 mmol) and solid pallete of KOH (20 mmol) was ground with a mortar and pestle for 15 minutes at room temperature. The obtained solid mixture was diluted with cold water, acidified with cold HCl (10%), followed by drying over anhydrous Na₂SO₄. The bromochalcone synthesized were characterization used by GC-MS.

3. Results and Discussion

The composition of the reagents for the synthesis of bromochalcone refers to [3] The mole of each reagent used is 0.01 moles, while the base mole is 0.02 moles. In stoichiometry, it only takes 0.01 mol, but based on research to produce the product, it takes two basic moles of reagent moles. The use of KOH twice the mole of reagents can increase the impact so that the chance of reaction is greater. Therefore, the mole of KOH used as a catalyst for bromochalcone synthesis is twice the mole of reactants.

Based on the stoichiometric concept, the mass of reagents used were 4-bromoacetophenone 1.99 g, 4-methoxy benzaldehyde 1.36 g, 3,4-dimethoxybenzaldehyde 1.66 g, 3,4,5-trimethoxy benzaldehyde 1.96 g, and KOH 1.12 g.

Synthesis of 4'-bromo-4-methoxichalcone (Chalcone 1) was started by mixing 4-bromoacetophenone, 4-methoxy benzaldehyde and KOH into pestle mortar and then grinding at room temperature for 15 minutes to obtain orange yellow solids. During these 15 minutes it is estimated that the reaction has taken place perfectly [3]. The reaction time in the grinding technique is shorter because there are many collisions at a faster speed between the reactant molecules and the amount of heat produced due to the friction of the reactant molecules during the grinding process.

4'-bromo-3,4-dimethoxichalcone (Chalcone 2) was synthesized in the same way, using 4-bromoacetophenone, 3,4-dimethoxy benzaldehyde and KOH, while for synthesis 4'-bromo-3,4,5-trimethoxichalcone (Chalcone 3) using 4-bromoacetophenone, 3,4,5-trimethoxy benzaldehyde and KOH. The synthesized Chalcone 1 in the form of pale white crystals is rather orange, Chalcone 2 in the form of yellow solids, while Chalcone 3 is in the form of a greenish yellow solid.

The mechanism of reaction of chalcone synthesis that occurs is as follows:

Stage I: Formation of carbanion from 4-bromoacetophenone
The first reaction stage is the formation of carbanion or enolate ions. 4-bromoacetophenone is an aromatic ketone which has hydrogen α. If treated with alkaline solutions such as KOH, the hydroxide ion from the base will attack hydrogen α from the ketone so that a carbanion is formed which can be stabilized by resonance and release the H₂O molecule.

Stage II: Nucleophilic addition reactions

The second reaction stage is a nucleophilic addition reaction. Nucleophilic reactions occur when nucleophilic (an excess electron compound) attacks an atom of another compound and forms a new compound. At this stage the enolate or carbanion ion formed at stage 1 acts as a nucleophile that attacks the carbonyl group of benzaldehyde. An alkoxide ion is formed which has an excess of electron charge in the O atom.

Stage III: Formation of an aldol

The third reaction stage is the formation of an aldol. Aldol is a compound formed from aldehydes and ketones where aldol takes protons from solvent molecules, H₂O. Alkoxide ions take hydrogen protons from H₂O molecules to form β-hydroxyketone (aldol). Then the hydroxide ion from H₂O binds to the potassium ion and returns to form a KOH base catalyst.

Stage IV: Dehydration reaction of aldol compounds

The fourth reaction stage is the dehydration reaction of the aldol compound. Dehydration reaction is a reaction of the release of water molecules. Carbonyl β-hydroxy like aldol is easily dehydrated, because the double bonds in the compound conjugate with the carbonyl group. According to [9], if dehydration produces a double bond that conjugates with an aromatic ring, dehydration takes place spontaneously. The β-hydroxyketone compound has hydrogen α to the carbonyl group which causes...
hydrogen α to be easily released in an alkaline atmosphere so that it can accelerate the dehydration of the aldol compound. The product is stable because there are double bonds conjugated with an aromatic ring. The dehydrated aldol compounds (loss of water) will form conjugated α, β unsaturated ketones or chalcone.

Overall the Claisen-Schmidt condensation reaction for bromo chalcone synthesis can be written as follows:

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\begin{align*}
\text{Bromo acetophenone} + \text{Benzaldehyde} & \rightarrow \text{Bromo chalcone} \\
\end{align*}
\]

Characterization of synthesized compounds using GC-MS. Chalcone 1 gives a chromatogram with 3 peaks. The highest and dominant peak is the third peak with a tR of 37.7 minutes (Figure 1). The peak was identified as the peak of the chalcone 1, as evidenced by mass spectra showing the presence of molecular ions (M+) at m/z 316. This interpretation is supported also from the m/z analysis in theory using ChemDraw, m/z Chalcone 1 appears on m/z 316.01 (100.0%), 318.01 (97.7%), 317.01 (17.4%), 319.01 (17.1%), 320.01 (1.8%), 318.02 (1.4%).

Mass spectra analysis of Chalcone 1 shows fragmentation peaks, 348; 331; 317; 303; 288; 267; 223; 196; 191; 181; 152; 119; 105; 89; 76; 63; 51; 39; and 28. Fragmentation of Chalcone 1 shows molecular ions (M+) releasing radical Br to form fragments with m/z 267. Fragment m/z 191 is the result of radical release of C₆H₄Br, while the m/z 164 fragment results from radical release of C₆H₄O₂. Molecular ion fragmentation releases C₆H₅O radicals giving fragments with m/z 191, while radical release C₁₀H₁₁O₂ produces fragments m/z 121.

**Figure 1. GC-MS Spectra of Chalcone 1**

GC-MS Chalcone 2 analysis provided GC chromatogram as shown in Figure 2. The chromatogram showed 3 peaks, the third peak as the dominant peak. The third peak has a retention time of 40.71 minutes and an area of 46.88%. MS analysis shows that the third peak is Chalcone 2 with m/z 348. The m/z analysis with ChemDraw analysis gives data m/z 346.02 (100%), 348.02 (97.9%), 347.02 (18, 5%), 349.02 (18.2%), 348.03 (1.6%), 350.03 (1.6%). Based on the ChemDraw analysis of m/z 348 compounds formed by 97.9% greater than molecular weight of Chalcone 2, that is at m/z 347, only obtained by 18.5%. The results of the GC-MS analysis concluded that the Chalcone 2 had been formed.

Molecular ion fragmentation Chalcone 2 (m/z 376) releases the OCH₃ radical and forms a cation with m/z 345. If the c radical is released, a cation will be formed with m/z 297. Then by releasing C₁₁H₁₅O₃
radical, a cation is formed with m/z 183, whereas cation with m/z 155 can be formed by releasing \( \text{C}_{12}\text{H}_{13}\text{O}_{4} \) radical.

Figure 2. GC-MS Spectra of Chalcone 2

Chromatogram Chalcone 3 (Figure 3) shows 3 peaks, with peaks dominant at the third peak, area of 52.88%.

The MS analysis shows that the Chalcone 3 has m/z 376. The price of m/z is similar to the molecular weight of Chalcone 3 (377). The difference in MR and m/z can be checked using the ChemDraw application. ChemDraw application can help analyze the price of m/z from a compound, the price of m/z is more than one. This is because of the difference in abundance in each of the atoms that make up the molecule. Based on ChemDraw's analysis, m/z Chalcone 3 is 376.03 (100%); 378.03 (97.3%); 377.03 (19.5%); 379.03 (19.1%); 378.04 (2.7%); 380.04 (1.8%). Based on ChemDraw analysis, m/z 376.03 is the one with the highest relative abundance, this is in accordance with the m/z that appears on the MS spectra, 376.

Chalcone 3 gives fragmentation by releasing OH radicals to form fragments m/z 283. Fragments with m/z 269 are fragments resulting from the release of radical OCH\(_3\), while fragments m/z 121 result from radical release of \( \text{C}_{10}\text{H}_{11}\text{O}_{2} \). Fragmentation of molecular ions by releasing \( \text{C}_{7}\text{H}_{3}\text{O}_{2} \) radicals produces m/z 164 fragments.

Figure 3. GC-MS Spectra of Chalcone 3
4. Conclusion

The bromochalcone derivatives (4'-bromo-4-methoxychalcone, 4'-bromo-3,4-dimethoxychalcone, 4'-bromo-3,4,5-trimethoxychalcone) can be synthesized from 4-bromoacetophenone and appropriate methoxy benzaldehyde through a green chemistry approach with grinding techniques.

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