Study of Citronellal Condensation Reactions with 1,2-phenylenediamine by CuSO$_4$ Catalyst under Microwave Irradiation

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Abstract. Benzimidazole compounds were prepared from the condensation reaction between 1,2-phenylenediamine and citronellal. In all cases, the condensation reaction is very selective and simple method under microwave conditions. The reaction takes place efficiently in ambient conditions with good results. Citronellal was used as the starting material for the synthesis of benzimidazoles because of their antibacterial activity. The strength of benzimidazole activity not only influenced by its main ring but also by the presence of substituents that bound to imidazole or aromatic ring. In this work, the purification of citronellal from kaffir lime oil was conducted by using salt reaction with NaHSO$_3$ saturated solution and hydrolysis by NaOH saturated solution. The synthesis reaction proceeds using CuSO$_4$ catalyst in dichloromethane as a solvent with mole ratio variation of 1,2-phenylenediamine to citronellal, 1:2, 1:3, 1:4, and 1:5, respectively. The optimum reaction was obtained at 1:2 and 1:3 mole ratio of citronellal. The yield of the product is 5.76 % and 5.097 % (m.p 140-143°C). FTIR analysis showed spectrum bands for C=N at 1671 cm$^{-1}$ and C-N 1269 cm$^{-1}$. Characterization was carried out using MS and showed that the synthesized product had a molecular weight m/z: 243, 381 and 453. Analysis result from FTIR, mass spectrometry and melting point indicated the product of benzimidazole derivatives was successfully obtained in this study.

Keyword: benzimidazole, citronellal, microwave, kaffir lime.

1. Introduction
The essential oil or volatile oil is one of the chemical compounds of plants that have a flavor. One of the essential oils that can be produced from Indonesian plants is kaffir lime [1]. Citronellal is the main compound contained in kaffir lime oil [2]. Kaffir lime oil also contains small amounts of other compounds such as linalool, citronellyl acetate, citronellol and geraniol [2,3]. Citronellal can be classified as a compound that has relatively high antibacterial activity. Based on the number of components in kaffir lime oil, this oil has the potential to be used as medicinal ingredients [4].

A structural modification was carried out by the addition of benzimidazole compounds which also have the potential as antibacterial substances. [5] Benzimidazole compounds are heterocyclic organic compounds that have an important role in medicinal. This compound consists of benzene rings...
attached to imidazole [6]. In general, the molecular skeleton of benzimidazole can be produced by a condensation reaction of 1,2-phenylenediamine compounds and carboxylic acids or aldehydes. Under certain conditions, the aldehyde group can react with 1,2-phenylenediamine to form 2-substituent benzimidazole. The reaction can be carried out by the Weidenhagen method, which is a reaction between aromatic amines and aldehydes in a solution of water or alcohol with copper salts [7].

According to the previous research, various derivatives of benzimidazole with 2-substitution can be synthesized by one-step reaction process using a condensation reaction of 1,2-phenylenediamine with various aromatic acids using a molar ratio of 1:1[8]. This method produced high yield product. Moreover, the synthesis of 2-benzimidazole substitutions by reacting o-phenylenediamine with aromatic, aliphatic and heterocyclic carboxylates using a microwave aid without using solvents with alumina catalyst, silica gel or HY zeolite is possible [9]. Furthermore, the synthesis of 1,2-substituted benzimidazole can be achieved by catalysis of SiO\textsubscript{2}/ZnCl\textsubscript{2} under solvent-free conditions at room temperature and under microwave (MW) irradiation [10].

From the explanation described above, most of the basic ingredients used are derived from petroleum and the chemical industry, especially non-renewable materials, toxic, flammable substances that are harmful to health and the environment [11]. Another approach that has been developed is the synthesis of drugs using natural ingredients. There are several reasons to use natural ingredients, which are quite abundant in nature, renewable, does not produce dangerous by-products, and the availability of structural diversity. One natural ingredient that can be used and available is very abundant is kaffir lime essential oil [12]. In addition, the use of microwaves is currently being developed in the method of benzimidazole synthesis. Microwave technology can help to reduce hours to minutes with high yield results, so the reaction becomes more efficient and economical [10]. Microwave-assisted synthesis of benzimidazole derivative from citronellal in Kaffir lime oil (Citrus hystrix DC.) increased 157.81 times compared by conventional heating using methanol solvent, however the percentage of yield only 0.77 times of synthesis using dichloromethane solvent [13].

2. Materials and Method

2.1. Materials
Kaffir lime (C. hystrix DC.) oil, 1,2-phenylenediamine was obtained from Sigma-Aldrich. Dichloromethane solvent, sodium bisulfite (NaHSO\textsubscript{3}), NaOH, and ethanol were provided from Merck Chemical Company.

2.2. Method

2.2.1. Purification of citronellal compounds in kaffir lime oil. One mole (30 mL) of citronellal contained in kaffir lime oil was placed in Erlenmeyer and added with 1.5 mol (23 mL) of saturated sodium bisulfite (NaHSO\textsubscript{3}), then stirred with a magnetic stirrer for 15 minutes. After a few minutes, it was then filtered with a Buchner funnel and washed with ethanol.

Each sediment obtained from the isolation process was placed in a beaker glass and hydrolyzed by the addition of 10% NaOH until the precipitate was completely dissolved, during the addition of 10% NaOH, the sediment was stirred for 15 minutes with a magnetic stirrer. After that, each solution was placed in a separatory funnel and allowed to stand for 5-10 minutes. The oil phase and the solvent phase is separated, then the oil phase was stored for analysis. This treatment was repeated to obtain as many isolates as used for the synthesis process.

2.2.2. Synthesis of Benzimidazole Derivatives. The synthesis of benzimidazole derivative compounds was adopted from the procedure used by Jacob et al. (2009) [10] which has been modified by variation of the citronellal and 1,2-phenylenediamine moles, using CuSO\textsubscript{4} catalysts and using citronellal compounds as a result of isolation from kaffir lime oil. The synthesis process was started by mixing 1,2-phenylenediamine and citronellal isolates with variations in the mole ratio of 1:2, 1:3, 1:4 and 1:5.
into a flat round bottom. Each mixture was added by 5 mL dichloromethane and 0.01 g CuSO₄ catalyst. The reaction was carried out in a microwave oven (LG 1200W 245 MHz) for 40 minutes. The mixture was then cooled for 3 days at cold temperatures to form crystals. The crystals formed were filtered and washed with cold dichloromethane solvents until white precipitate obtained. Crystals were then dried and stored at room temperature.

2.2.3. Analysis of chemical composition and product synthesis. The analysis of the essential oil was performed on Gas Chromatography-Mass Spectrophotometry (GC-MS) on Agilent 7890B (GC) and 5977B (MS). The GC peak areas were used to determine the percentage of product, and MS spectra to determine m/z. The IR spectra of the compounds were recorded on Perkin Elmer FT-IR spectrometer with KBr pellets. The inlet temperature was 200°C. Melting points of the synthesized compounds were determined on Electrothermal MEL-TEMP and MS characterization.

3. Results and Discussion

3.1. Purification of citronellal compounds in kaffir lime oil

Purification of citronellal compounds was carried out by salting reaction using sodium bisulfite (NaHSO₃) according to Figure 1. The reaction produced citronellyl bisulfite salts in the form of yellowish-white solid.

![Figure 1. Citronellal reaction with sodium bisulfite](image)

It can be appeared that in the reaction of Figure 1, the polar aldehyde group from citronellal acts as an electrophile and NaHSO₃ salts as nucleophiles, thus producing water-soluble salts. Other components of unreacted kaffir lime oil were separated from sodium-citronellyl-bisulfite salts by filtration using a Buchner funnel. The other components that still mixed with salt were washed with ethanol, so that the white salt of citronellyl bisulfite can be obtained.

The citronellyl bisulfite salt that obtained was hydrolyzed using 10% NaOH to obtain citronellal again. The hydrolysis of sodium citronellyl bisulfite salt occurs because alkaline hydroxy ions attacked the proton from the hydroxy salt group which resulted in anion resonance followed by the released of sulfide ions, resulting in citronellal production (Figure 2).

![Figure 2. Hydrolysis reaction with sodium hydroxide](image)

Based on the chromatogram in Figure 3, kaffir lime oil was composed of 15 components (Figure 3a) and according to the mass spectral analysis (Table 1) the highest peak with tR 15.909 minutes (m/z 154) is citronellal in 28.27% purity.
Figure 3. Chromatogram Results (a) Kaffir lime oil (b) Citronellal isolates

Table 1. Tabulation of the results of GC-MS analysis from kaffir lime oil and salting isolates.

| Peak Number | Retention time (minutes) | SI | Composition                  | Peak Number | Retention Time (minutes) | SI | Composition                  |
|-------------|--------------------------|----|------------------------------|-------------|--------------------------|----|------------------------------|
| 1           | 10.917                   | 98 | n-decane                     | 1           | 14.078                   | 98 | Linalool                     |
| 2           | 11.553                   | 87 | 2-butyl-1-octanol            | 2           | 15.532                   | 97 | 5-methyl-2-(1-methylethenyl)- cyclohexanol |
| 3           | 11.637                   | 93 | 4-methyldecane               | 3           | 15.909                   | 97 | Citronellal                  |
| 4           | 11.908                   | 92 | n-butylcyclohexane           | 4           | 16.302                   | 95 | 5-methyl-2-(1-methylethenyl)- cyclohexanol |
| 5           | 12.017                   | 91 | 3-methyldecane               | 5           | 16.535                   | 94 | Isopulegol                   |
| 6           | 12.148                   | 90 | 3,7-dimethylnonane           | 6           | 18.016                   | 99 | ß-Citronellol                |
| 7           | 12.633                   | 90 | trans-decahydropthalene      | 7           | 21.564                   | 96 | Citronelly acetate           |
| 8           | 12.747                   | 97 | 2,5-dimethylnonane           | 8           | 21.770                   | 98 | 2-methoxy-3-(2-propenyl)-phenol |
| 9           | 12.959                   | 94 | 2-methyldecane               |             |                          |    |                              |
| 10          | 13.165                   | 93 | 3-methyldecane               |             |                          |    |                              |
| 11          | 14.105                   | 91 | n-decane                     |             |                          |    |                              |
| 12          | 15.576                   | 97 | 5-methyl-2-(1-methylethenyl)- cyclohexanol |             |                          |    |                              |
| 13          | 15.807                   | 98 | Citronellal                  |             |                          |    |                              |
| 14          | 15.915                   | 96 | Isopulegol                   |             |                          |    |                              |
| 15          | 29.532                   | 85 | hexadecamethyl-cyclooctacycloxane |             |                          |    |                              |
Based on the chromatogram in Figure 3b, it can be seen that the results of citronellal isolation by salting method resulted in an increasing in purity which reached 87.95%. Some components that are still mixed with the citronellal component included linalool, 5-methyl-2-(1-methylethenyl)-cyclohexanol, 5-methyl-2-(1-methylethenyl)-cyclohexanol, isopulegol, β-Citronellol, Citronellyl acetate, 2-methoxy-3-(2-propenyl)-phenol (Table 1). These components are possible to have similar characteristics with citronellal compounds and get trapped in salt so that they are still detected even though they have very small levels. Based on these results, citronellal isolates were then used as the main ingredient in the synthesis process of benzimidazole derivatives to determine the effect of reactions that occurred on product formation.

3.2. Citronellal Condensation Reaction with 1,2-phenylenediamine

Benzimidazole derivatives were formed by citronellal condensation reaction using 1,2-phenylenediamine. The reaction was carried out using dichloromethane and CuSO₄ catalysts for 40 minutes and cooled in the refrigerator for 24 hours to obtain the solid. The solids were purified by washing using cold dichloromethane which is non-polar solvent, so it could dissolve the reactants. The product was already obtained when the solid turned into a whiter color. This indicates that other compounds that are still present in the product dissolve in dichloromethane while the benzimidazole derivative of a more polar is insoluble and produces a purer product, the results are shown in Table 2.

Table 2. Results of Benzimidazole Synthesis.

| Mole Ratio | % yield | melting point (°C) |
|------------|---------|--------------------|
| 1,2-Phenylenediamine: Citronella |        |                    |
| 1 : 2      | 5.76    | 140 – 143          |
| 1 : 3      | 5.097   | 139 – 143          |

Based on the variation of mole ratio, the reaction that produced benzimidazole was in moles variations 1: 2 and 1: 3, whereas in moles variation 1: 4 and 1: 5, the solids did not form. It might be occurred because there were still other components contained in citronellal isolates which interfere the product formation because of its impurity. By increasing the number of citronellal moles added to the reaction, the impurities can block the collision process between citronellal and 1,2-phenylenediamine to form the product.
The product was characterized by FTIR which showed the appearance of C=N at 1671 cm$^{-1}$ and C-N at 1269 cm$^{-1}$ which is indicated the formation of an imidazole group. Furthermore, the absorption at 1622 cm$^{-1}$ and 1427 cm$^{-1}$ indicated the presence of benzene groups. The disappearance of aldehyde (-CHO) peak and the loss of secondary and primary amines due to the substitution of citronellyl group. Mass Spectrometry (MS) was used for qualitative tests through identification of ion fragmentation of compounds and identified the mass ratio of the charge.

![FTIR Spectra of Product Synthesis](image)

Figure 4. FTIR Spectra of Product Synthesis

![MS Spectra of Product Synthesis](image)

Figure 5. MS Spectra of Product Synthesis
Figure 5 showed the fragmentation of the product with (m/z) 241, 381 and 453, respectively. Based on these results benzimidazole derivative compounds have been formed, with the presumed compound 2-dicitronellylbenzimidazole (241 m/z), 1,2-dicitronellylbenzimidazole (381 m/z) and 3-(2-buten-1-ol) -1,2-dicitronellylbenzimidazole (453 m/z) (Figure 6).

![Figure 6](image-url)

Figure 6. Alleged Benzimidazole Derivative Structure. (a) 2-sitronelilbenzimidazole (b) 1,2-disitronelil benzimidazole (c) 3-(2-buten-1-ol)-1,2-disitronelil benzimidazole

4. Conclusion
An improvement of benzimidazole derivative was successfully synthesized by the condensation between 1,2-phenylenediamine and citronellal from kaffir lime oil. This study showed the purity of citronellal isolates affects the formation of benzimidazole derivative products. In addition, the reaction time could be reduced from hours to minutes by using microwave.

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