

Microwave-assisted Synthesis of Benzimidazole Derivatives from Citronellal in Kaffir Lime (*Citrus hystrix* DC.) Oil

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Abstract. Benzimidazoles are an important group of heterocyclic aromatic organic compound in the field of medicinal chemistry. It plays a very important role in pharmacological activity such as, analgesic, antiinflammatory, antibacterial, anti ungai, anti iral, antihelmenthic, anti convulsant, antihypertensive, and antiulcer. The synthesis of benzimidazole derivative under microwave irradiation of citronellal as raw material which is extracted from *Citrus hystrix* DC. (kaffir lime) leaves. The reaction using methanol and dichloromethane as solvent with variation of reaction time at 30, 40, 50, 60, and 70 minutes and mole ratio of citronellal to 1,2-phenylenediamine, 1:1, 1:1.5, and 1:2, respectively. Synthesis products was characterized by FT-IR and GC-MS. The optimum reaction time was obtained at 60 minutes in the present of dichloromethane and 1:2 mole ratio of citronellal to 1,2-phenylenediamine. The yield of the product is 42.19%. Structure of the synthesized compound were assigned on spectrum bands for C=N str at 1661 cm⁻¹, C-N str at 1271 cm⁻¹, C=C str of benzene ring at 1622 and 1456 cm⁻¹ and C=C str of alkene at 1379 cm⁻¹. GC-MS analysis showed single peak with retention time of 15.339 minute and m/z 242.

1. Introduction

Benzimidazole is a heterocyclic organic compound, which important in medicinal chemistry. This compound is bicyclic compound which consist of benzene ring fused with imidazole, which possesses many pharmacological properties [1]. The most prominent benzimidazole compound in nature is N-ribosyl-dimethylbenzimidazole, which serve as an axial ligand for cobalt in vitamin [1, 2, 3]. Benzimidazoles were reported to have antimicrobial properties against bacteria or fungi [4]. Benzimidazole and its derivatives are reported to be physiologically and pharmacologically active and some applications are found in the treatment of several diseases including epilepsy, diabetes and infertility [5]. This important group of substances has found practical applications in a number of fields: analgesic [6,7,8], antiinflammatory [7,8,9,10], antibacterial [11], antifungal [12], antiviral [13,14], anti thelmenthic [15], anticonvulsant [16,17], anticancer [18,19], antiulcer [20], antihypertensive [21], drugs against parasites [22,23] while some derivatives have been synthesized and evaluated for inhibition of HIV-1 [24].



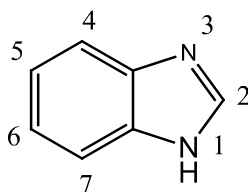


Figure 1. H-Benzimidazole

The efficient and economical methods to synthesis benzimidazole by condensation reaction between 1,2-phenylenediamine with various compounds in the presence of various reaction condition as reflux for 8h in ethanol, reflux for 1.5h in iodine/water, and using methanol proceeds at room temperature with only natural sources, molecular oxygen and visible light irradiation with blue LEDs [25]. Nowadays, microwave assisted organic synthesis is gaining widespread acceptance in drug discovery laboratories. Microwave technology, by accelerating chemical reactions from hours or days into minutes, provides quick results [26]. Saberi has reported synthesis of 2-benzimidazoles under microwave irradiation and solvent-free condition which is catalyzed by alumina, silica gel and zeolite HY the reaction mixture was then irradiated in a domestic microwave oven for 5-9 min at 160-560 W [27]. Nagula et al has reported Microwave-assisted synthesis caused a significant reduction in the reaction times and improvement in the yields of new benzimidazole bearing thiazolidinedione derivatives [28]. Current drug development is focused on compounds that are synthesized from natural materials. In this study, benzimidazole derivative from citronellal in kaffir lime oil were synthesized utilizing microwave assisted. The effect of reaction time and solvent was studied by comparing the yield of product.

2. Material and Methods

2.1. Materials

Kaffir lime oil was obtained from Essential Oil's Institute, Brawijaya University. The oil is extracted from a mixture of leaves and twigs with steam distillation. 1,2-phenylenediamine was provided by Sigma-Aldrich. Dichloromethane, and methanol solvents were provided by Merck Chemical Company and were used without further purification.

2.2. Methods

The kaffir lime oils were obtained by steam distillation of 375 Kg (w/w) 1:1 mixture between the leaves and twigs (w/w) 1:1 distilled with steam pressure 2.5-4 bar for 4h. The essential oil was characterized by refractometer, picnometer, FT-IR and GC analysis was performed on Agilent 5890, equipped with HP-608 (30m x 320 μ m i.d.; film thickness 0.50 μ m) capillary column. The carrier gas was nitrogen (velocity: 1.5 mL/minutes). The column oven temperature was programmed as follows: initial temperature 100 °C, 5 minute; ramp to 250 °C at 5 °C/minutes. Quantitative analysis of GC were used to determines the percentage of citronellal.

The synthetic strategy is illustrated in Fig. 3. The benzimidazole derivatives was synthesized by mixing 0.0065 mole of 1,2-phenylenediamine and 0.013 mole of citronellal (1:2) in 5 mL dichloromethane and reacted under domestic microwave oven (LG 1200W 245 MHz) for 60 minutes. The mixture was cooled to room temperature for 15 minutes and put in the refrigerator (-5 °C) for 24 hours. The crystals formed are filtered and washed with dichloromethane, dried at room temperature and stored. Variations of reaction time have been carried out at 30, 40, 50, 60, and 70 minutes. The mole ratio of citronellal and 1,2-phenylenediamine was modify at 1:1, 1:1.5, and 1:2 ratio. The reaction is also carried out using a methanol solvent.

2.3 Characterization of synthesized products

The IR spectra of the compounds were recorded on Perkin Elmer FT-IR spectrometer with KBr pellets. GCMS analysis was performed on Agilent 7890B (GC) and 5977B (MS), equipped with HP-5 MS capillary column. The inlet temperature was 200 °C. The carrier gas was helium (flow: 54.087

mL/minutes). The column oven temperature was programmed as follows: initial temperature 150 °C, 1 minute; ramp to 300 °C at 10 °C/minutes. GC peak areas were used to determine the percentage of product, and MS spectra to determine m/z.

3. Result and Discussion

3.1 Identification of kaffir lime oil

The kaffir lime oil gives the yellow liquid and have a fresh, aromatic, explosive fragrance which is floral and citrus-like. The refractive index, specific gravity, yield of distillation, percentage of citronellal are 1.439, 0.85 g/ml, 0.5% and 60.44%, respectively. The kaffir lime oil was characterized by FT-IR spectroscopy compared with standard citronellal spectrum (Fig. 2). It was found that there was a peak 1726 cm^{-1} (C=O stretching), 2922, 2874 cm^{-1} (C-H stretching of aldehyde) and 1454, 1379 cm^{-1} (C=C stretching of aromatic), similar with citronellal spectrum.

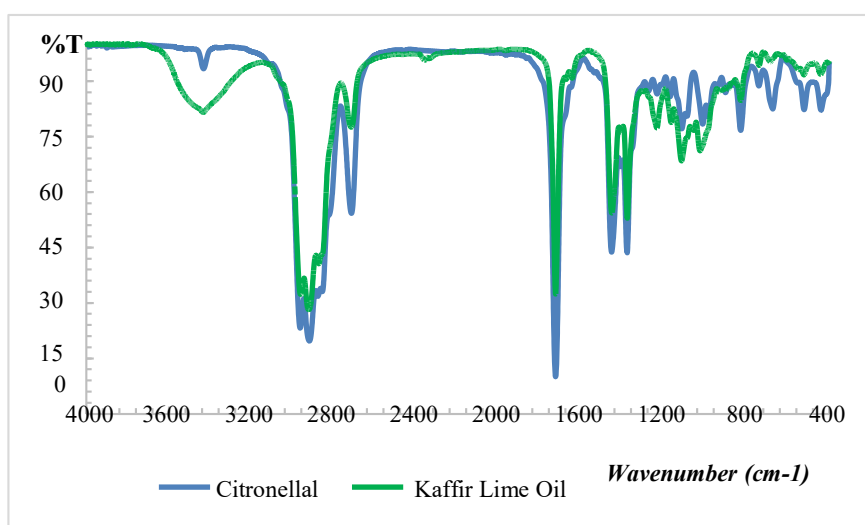


Figure. 2 Spectra of kaffir lime oil and citronellal

3.2 The synthesis of Benzimidazole Derivative

The benzimidazole derivative were synthesized by microwave assisted synthesis (Figure 3). When the reaction does not use a solvent, a crystal product is not formed. The products of benzimidazole derivative compounds synthesized using dichloromethane solvent appear purer in the form of white crystals, while using methanol obtained yellow crystals (Fig. 4). The condensation reaction of 1,2-phenylenediamine with citronellal requires the medium to interact, therefore the reaction carried out without the use of the solvent does not produce the product in solid form, its different when the reaction using a solvent. Methanol is a more polar solvent than dichloromethane, in which solvent polarity affects the product. in this case the solvent with high polarity is not suitable as a medium of interaction between molecules, so the resulting product is not pure (Fig 4.a). Otherwise when using a less polar solvent can produce products with high purity.

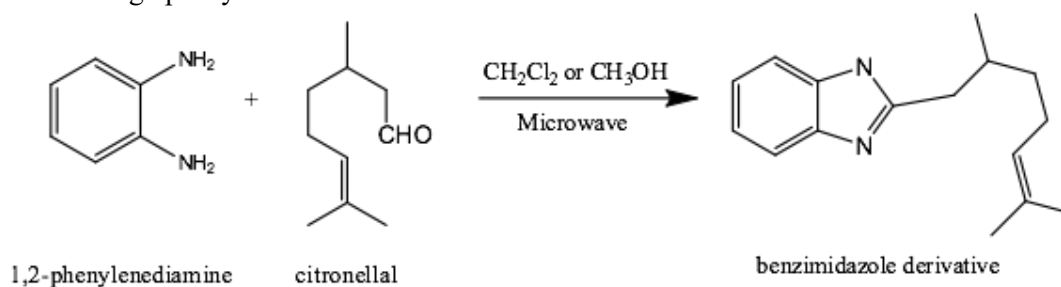


Figure 3 The synthesis of benzimidazole derivative from citronellal



Figure 4. Product of benzimidazole derivative in : (a) methanol (b) dichloromethane

The structures of the synthesized compounds were confirmed using FTIR (Fig. 5), and GC-MS (Fig. 6). Characteristics of benzimidazole derivative from FTIR spectra (Fig. 5) contained a distinctive band at 1661 cm^{-1} and 1271 cm^{-1} as C = N str and C-N str of imidazole group, C = C str of benzene group at 1622 cm^{-1} and 1456 cm^{-1} , C = C str of alkene group at 1379 cm^{-1} and the character peak of aldehyde (C=O) was missed due with the reaction. GC-MS analysis showed single peak (tR 15.339 minute) and m/z 242.2 as molecular ion (M^+) and m/z 145 as base peak of spectra mass (Fig 6).

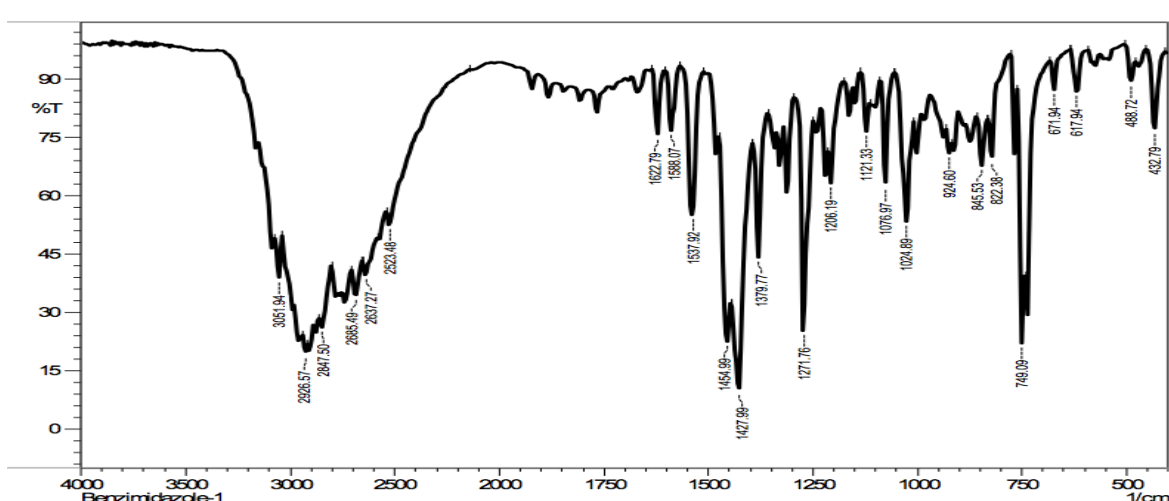


Figure 5 IR spectra of synthesized product

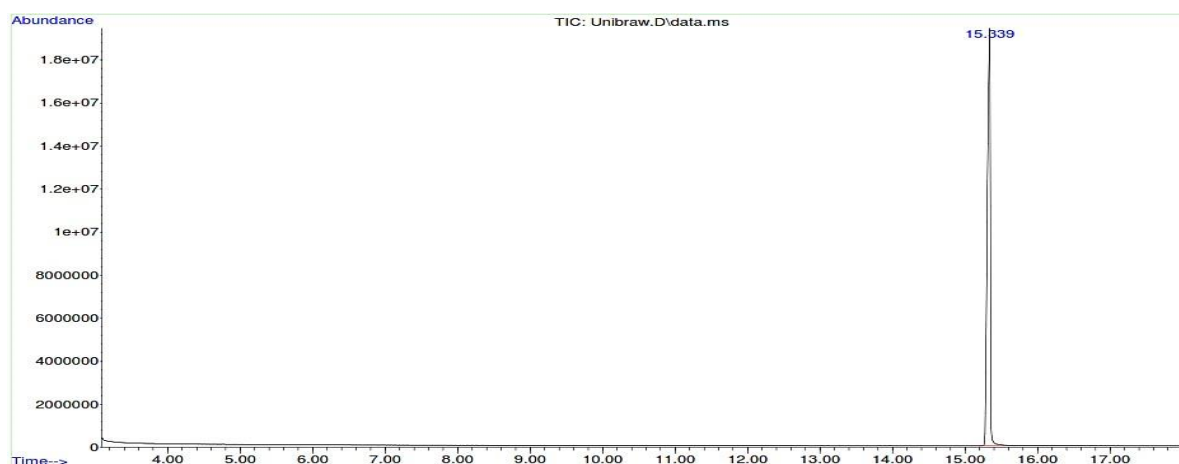


Figure 6 GCMS spectra of synthesized product

The comparative data of the synthesized compounds are provided graph in Fig. 7. The result shows the time required to react the whole compound using microwave irradiation is 30 to 70 minutes in the presence dichloromethane and methanol. The yield of benzimidazole derivative by dichloromethane solvent increased significantly and is greater than methanol solvent. The time optimum of microwave-assisted synthesis using dichloromethane solvent at 60 minute with yield 19.23%. When the reaction conducted in the presence of methanol at 50 min gave 18.59%.

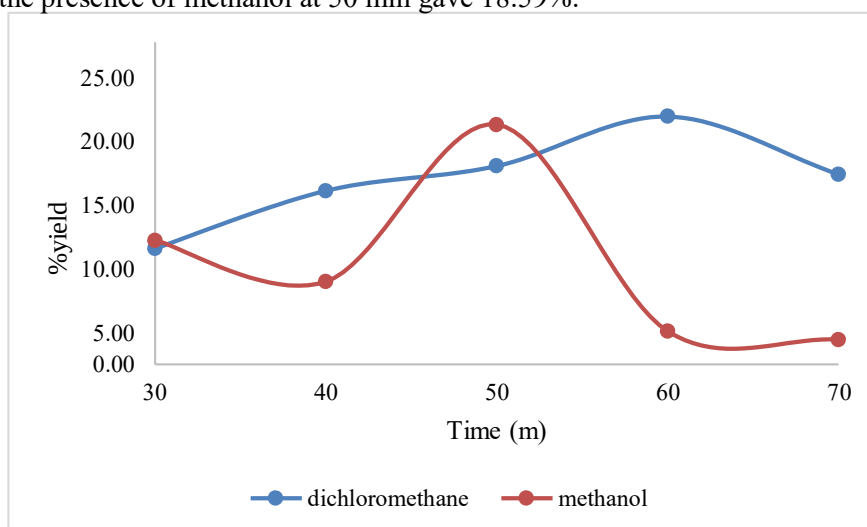


Figure 7 Variation of solvent in the synthesis of benzimidazole derivative

In addition, the time optimum of microwave-assisted synthesis using dichloromethane solvent at 60 minute is used at variations of mole ratio of citronellal to 1,2-phenylenediamine, respectively 1:1, 1:1.5, and 1:2 shown in Table 1. The optimum reaction time of microwave-assisted synthesis using dichloromethane solvent at mole ratio 1:2 with yield 42.19% shown in Table 1. The number of mole ratio starting material will affect the resulting product, the more moles of 1,2-phenylenediamine increasing the amount of product with a fixed mole of kaffir lime oil.

Table 1. Optimization of the synthesis of benzimidazole derivative from citronellal ^a

Entry	Mole ratio		CH ₂ Cl ₂ (mL)	Time (minutes)	Yield (%)
	Kaffir lime Oil	1,2-phenylene diamine			
1	1	1	-	60	NR ^b
2	1	1	5.0	60	10.94
3	1	1.5	5.0	60	16.41
4	1	2	5.0	60	42.19

^a Reaction conditions: using microwave assist on the reflux process (frequency 2450 MHz, wattage 1200W, cavity temperature 120 °C)

^b No crystal was formed

4. Conclusion

The optimum yield of benzimidazole derivative which was synthesis by condensation between citronellal and 1,2-phenylenediamine under microwave irradiation is 42.19% at 60 minutes and 1:2 mole ratio using dichloromethane solvent. Further studies have to be carried out to test the antibacterial activity of benzimidazole derivative synthesized from citronellal.

Acknowledgments

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