

Comparison of Conventional and Microwave-assisted Synthesis of Benzimidazole Derivative from Citronellal in Kaffir lime oil (*Citrus hystrix* DC.)

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Abstract. Simple method has been used for the synthesis of benzimidazole derivative from citronellal in kaffir lime oil under microwave irradiation. These compounds were synthesized also by conventional heating for comparison. In addition, microwave-assited synthesis was also compared between using to dichloromethane and methanol solvents with variation of reaction time for 30 to 70 minutes and 4 to 12 h for conventional heating. The 2-citronellyl benzimidazole compound synthesized were characterised by FT-IR, GC-MS, ¹H and ¹³C NMR spectroscopy. Comparison between conventional and microwave-assisted synthesis was done by comparing between correlation of reaction time and percentage yield. The time optimum of microwave-assisted and conventional synthesis using dichloromethane solvent respectively at 60 minutes (yield 19.23%) and 8 hours (yield 11.54%). In addition, microwave-assited synthesis increasing 157.81 times compared by conventional heating. While using methanol solvent tends to increase linearly however the percentage of yield only 0.77 times of synthesis using dichloromethane solvent.

1. Introduction

Benzimidazole, a fused heterocycle bearing benzene and imidazole has gained considerable attention in the field of contemporary medicinal chemistry. The moiety is of substantial importance because of its wide array of pharmacological activities [1]. At the core of these molecules have basic and acidic characters that can form salts with different acids. Optimization of the structure of benzimidazole has been widely practiced, such as changes in substituents in aryl groups, benzyl groups and or indole groups that can provide various bioactivity [2].

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 [3]. These compounds show a wide range of biological activities like anti-inflammatory as well as analgesic activity [4,5], antibacterial and antifungal [6,7], antitubercular [6], antiviral [8], anthelmintic and antiproliferative [9,10], antimalarial [11], antiulcerative, antioxidant [12,13], antiproliferative [14], antihypertensive [15, 16], antitumor [17,18]. Some benzimidazoles have also been



evaluated as cholinesterase inhibitors [19,20], drugs against parasites [21,22] while some derivatives have been synthesized and evaluated for inhibition of HIV-1 [23].

The efficient and economical methods of synthesizing benzimidazole by condensation reaction between ortho phenylene diamine and various compounds in the presence of various reaction condition [24]. Nowadays, microwave-assisted organic synthesis is gaining widespread acceptance in drug discovery laboratories. Microwave technology, by accelerating chemical reactions from hours or days to minutes, provides quick results [25]. In this study, benzimidazole derivative of citronellal in kaffir lime oil were synthesized utilizing both microwave and conventional methods. The performance of two methods was compared and studying the reaction kinetics.

2. Material and Methods

2.1 Materials and Instrumentation

The kaffir lime oil was obtained from Essential Oil's Institute, Brawijaya University. The products were prepared by steam distillation.

All chemicals and solvents were supplied by Sigma Aldrich and were used without further purification. Microwave reaction was carried out in domestic microwave oven (LG 1200W 245 MHz). GC/MS 5977 Agilent Tech. with HP-5MS capillary column used to make TIC and mass spectra. Nuclear magnetic resonance (NMR) spectra were recorded on JEOL ECS 400 MHz NMR spectrometer using methanol d₄ as solvent. Chemical shifts were reported in parts per million relative to internal standard tetramethylsilane. IR spectra of the compounds were recorded on Perkin Elmer FT-IR spectrometer with KBr pellets.

2.2 Methods

The Essential Oil Extraction

The kaffir lime oils were obtain by steam distillation. 375 kg of leaf and twig mix (w/w) 1: 1 distilled with vapor pressure 2.5-4 bar for 4h. The essential oil was characterized by refractometer, picnometer and GC type HP 5895 with HP-5MS capillary column.

Conventional Method

A mixture of 6.0 mL of kaffir lime oils (5.1 g), 1.4 g o-phenylenediamine and 10 mL dichloromethane were fed into a round bottom flask. The reflux condensation was carried out for 4 hours. Then, the mixture was cooled to room temperature and the nex cooled in the refrigerator for 24 hours. The crystals are filtered and washed with cold dichloromethane, dried in air and stored. Variations of reflux condensation have been done for 4, 6, 8, 10, 12 and 14 hours.

Microwave Method

A mixture of 6.0 mL (5.1 g) of kaffir lime oils, 1.4 g o-phenylenediamine and 10 mL dichloromethane were fed into a round bottom flask and microwaved at 1200W for 60 min. The reaction was monitored by TLC silica with ethylacetate: n-hexane: methanol (3: 2 : 1) as eluent. Then, the mixture was cooled to room temperature and then kept in the refrigerator for 24 hours. The crystals are filtered and washed with cold dichloromethane, dried in air and stored. Variations of reaction time in microwave have been done for 30, 40, 50, 60 and 70 minutes. Another variation in synthesis used methanol solvent.

3. Result and Discussion

Kaffir lime oil as a citronellal source was obtained from steam distillation. The characteristic of kaffir lime oil that is liquid yellow with unique aromatic scent and refractive index, specific gravity, percentage of rendemen, percentage of ccitronellal are 1,439; 0.85 g/ml, 0.5% and 60.40% respectively.

2-Citronellyl benzimidazole were synthesised by both conventional synthesis and microwave-assisted synthesis by synthetic schemes (Fig. 1). The products of benzimidazole compounds

synthesized using dichloromethane solvent appear purer in the form of white crystals, while using methanol obtained yellow crystals. The structures of the synthesized compounds were confirmed using IR, GC-MS and NMR. Character of benzimidazole compound synthesized on the IR spectra 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} and (C = C str) of alkene group at 1379 cm^{-1} . GC-MS analysis showed pure (tR 15.339 minute) and m/z 242 as molecular ion (M^+) and m/z 145 as base peak of mass-spectra. The NMR spectroscopic character exhibited ^1H -NMR and ^{13}C -NMR were characterized by 11 proton spectra types and 16 carbon-13 spectra as shown in Fig.2.

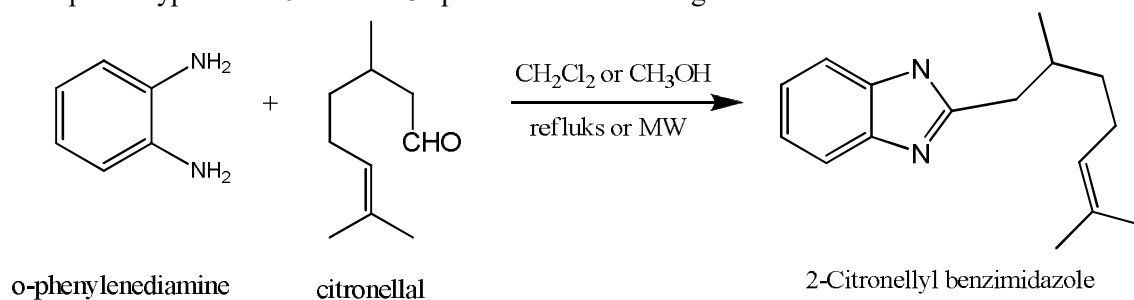


Fig. 1 Synthesis benzimidazole derivative compound

The comparative data of the synthesized compounds are provided graph in Fig.3. The reaction time for the synthesis of all compounds by conventional heating methods was 4 to 10 h, in comparison with the microwave heating (30-60 min), an obvious many-fold time reduction. Overall approximately, the rate of synthesis of benzimidazole by microwave method is greater than the conventional heating method. The time optimum of microwave-assisted syntheses using dichloromethane solvent at 60 minute with yield 19.23% and increase 157.81 times compared by conventional hating.

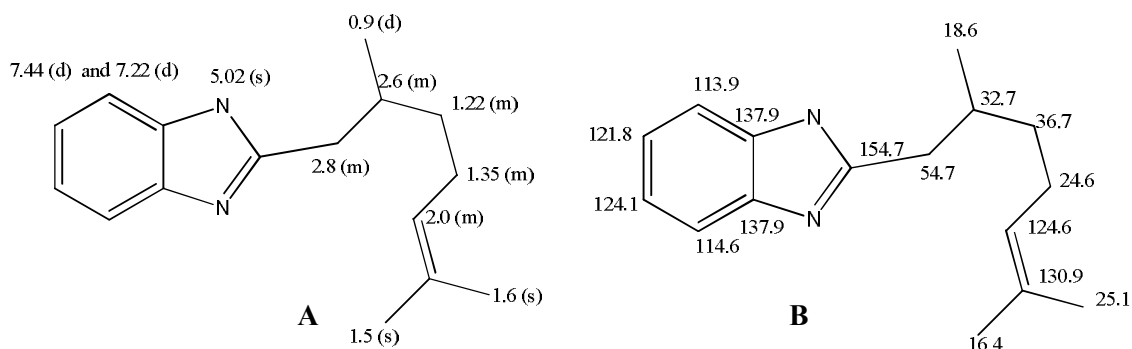


Fig 2. NMR spectra pattern of 2-citronellyl benzimidzole
 A. δ (ppm) of ^1H -NMR spectra B. δ (ppm) of ^{13}C -NMR

In addition, the microwave-assisted synthesis using methanol tends to increase linearly with increasing reaction time with percent yield only 0.77 times of synthesis using dichloromethane solvent.

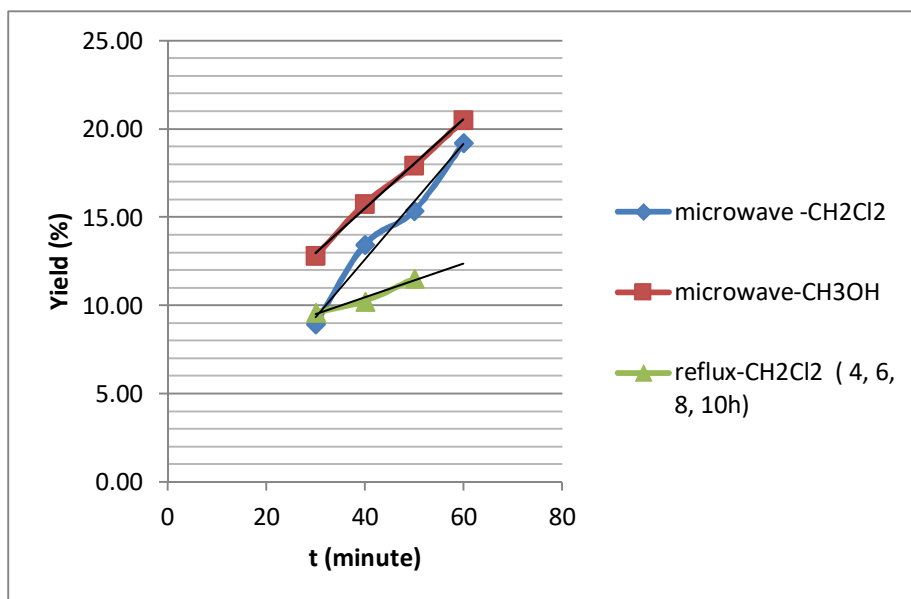


Figure 3. Correlation of time reaction and % yield of 2-Citronellyl benzimidazole synthesis

4. Conclusion

The time optimum of microwave-assisted and conventional synthesis using dichloromethane solvent respectively at 60 minutes (yield 19.23%) and 8 hours (yield 11.54%). In addition, the microwave-assisted synthesis increasing 157.81 times compared by conventional heating. While using methanol solvent tends to increase linearly however the percentage of yield only 0.77 times of synthesis using dichloromethane solvent.

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