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GREEN SYNTHESIS OF DEHYDROZINGERONE (DHZ) UTILIZING IONIC LIQUID MEDIUM AND MICROWAVE IRRADIATION

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Abstract: Dehydrozingerone (DHZ), 4-(4-hydroxy-3-methoxyphenyl)-3-buten-2-one, a natural compound found in the rhizome of ginger plants (*Zingiber officinale*), exhibits a wide range of bioactivities, including antioxidant, anticancer, antimalarial, antidepressant, antifungal, and many other bioactivities. Conventionally, DHZ is synthesized through a cross-aldol Claisen-Schmidt condensation of vanillin and acetone, but this process often requires extended reaction times (up to 48 hours), results in low yields, and involves the excess use of organic solvents for purification. To address these limitations, this study aims to develop a green synthesis method for DHZ utilizing a 1-decyl-3-methylimidazolium bromide ([DMIM]Br) ionic liquid medium and microwave-assisted organic synthesis (MAOS) method. The experimental procedure involved optimizing the reaction conditions and varying the concentration of [DMIM]Br under microwave irradiation. Product characterization was performed by melting point determination, thin-layer chromatography (TLC), Fourier transform infrared (FTIR), and nuclear magnetic resonance (NMR) ^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) spectroscopy. These findings indicate that the use of the [DMIM]Br ionic liquid significantly improved the purity and yield of DHZ products. The optimal conditions were synthesis from vanillin and acetone in a 1:10 molar ratio, 2.5 M NaOH, and 5% [DMIM]Br (w/v) using MAOS for 120 minutes (50°C, 300 W) to produce a 62.96% yield product in the form of a bright yellow solid with a melting point range of 129–130°C. The use of ionic liquids and MAOS provides a more efficient and environmentally friendly method for synthesizing DHZ, offering a significant reduction in reaction time and eliminating excess organic solvents, thus making it a promising alternative to traditional synthesis methods.

Keywords: Dehydrozingerone (DHZ), Green Chemistry, Ionic Liquid, Microwave Synthesis

Abstrak: Dehidrozingeron (DHZ), 4-(4-hidroksi-3-metoksifenil)-3-buten-2-on, merupakan senyawa alam yang terdapat pada rimpang jahe (*Zingiber officinale*) yang menawarkan berbagai potensi bioaktivitas termasuk antioksidan, antikanker, antimalaria, antidepresan, antijamur, dan masih banyak lainnya. Sintesis DHZ secara konvensional dapat dilakukan melalui kondensasi aldol-silang *Claisen-Schmidt* dari vanilin dan aseton, namun proses ini sering kali membutuhkan waktu reaksi yang lama (hingga 48 jam), menghasilkan produk dengan rendemen rendah, dan melibatkan penggunaan pelarut organik yang berlebihan untuk pemurnian. Untuk mengatasi keterbatasan ini, penelitian ini bertujuan untuk mengembangkan metode sintesis DHZ yang lebih hijau dengan menggunakan media cairan ion 1-desil-3-metilimidazolium bromida ([DMIM]Br) dan metode Sintesis Organik berbantu Gelombang Mikro (MAOS). Prosedur eksperimen melibatkan optimalisasi reaksi dengan variasi persentase [DMIM]Br dengan bantuan iradiasi gelombang mikro. Karakterisasi produk dilakukan dengan menggunakan penentuan titik leleh, kromatografi lapis tipis (TLC), dan spektroskopi FTIR, spektroskopi resonansi magnetik inti (NMR) ^{1}H (500 MHz, $CDCl_3$) dan ^{13}C (125 MHz, $CDCl_3$). Hasil penelitian menunjukkan bahwa penggunaan cairan ion [DMIM]Br meningkatkan kemurnian dan rendemen produk DHZ. Kondisi optimal dicapai dengan menggunakan vanilin dan aseton dalam rasio molar 1:10, NaOH 2,5 M, dan [DMIM]Br 5% (w/v) menggunakan MAOS selama 120 menit (50°C, 300 W), menghasilkan produk dengan rendemen 62,96% dalam bentuk padatan kuning terang dengan rentang titik leleh 128–129°C. Penggunaan cairan ion dan MAOS menawarkan pengurangan waktu reaksi yang signifikan dan pengurangan penggunaan cairan pelarut berbahaya secara berlebihan, sehingga menjadikannya metode alternatif yang menjanjikan dibandingkan dengan metode sintesis tradisional.

Kata kunci: Dehidrozingeron (DHZ), Kimia Hijau, Cairan Ion, Sintesis Gelombang Mikro

INTRODUCTION

Dehydrozingerone (DHZ), also known as 4-(4-hydroxy-3-methoxyphenyl)-3-buten-2-one, is a naturally occurring compound that can be extracted from the rhizome of ginger (Zingiber officinale). This compound has gained significant attention from researchers, particularly in the field of medicinal chemistry. DHZ is recognized as a half-structural analog of curcumin with one carbonyl functional group. Curcumin possesses various biological activities and is widely utilized for its anticancer properties. However, its limited solubility and bioavailability present challenges to its pharmacological effects (Mapoung et al. 2020). In recent studies, scientists have shown enormous interest in DHZ and its derivatives. Consequently, DHZ has been recognized as a promising scaffold for the development of potentially valuable drugs with a wide range of biological activities (Hampannavar et al., 2016; Kumar et al., 2022). With these unique structural features, DHZ has been found to have several potential bioactivities including antifungal (Yamano et al. 2023), anti-inflammatory, antioxidant, and wound healing properties, making it effective in the treatment of diabetic foot ulcers (DFUs) (Begum et al. 2023). Additionally, DHZ has been shown to inhibit prostate cancer progression in vitro and in vivo, with the potential to improve the bioavailability of curcumin (Mapoung et al., 2020).

The laboratory synthesis of DHZ can be achieved through a simple aldol condensation reaction between vanillin and acetone. However, this synthesis process can be challenging, and several methods have been reported in the literature. One of the main challenges in DHZ synthesis is the lack of highly efficient and selective synthesis methods for the formation of key intermediate. At room temperature, the synthesis of DHZ requires a reaction time of 24–48 hours, resulting in a product yield ranging from 33% to 50% (Abdelrahman 2017; Hayun et al. 2018). In a previous study by Ruiz et al. (2020), alternative methods for DHZ synthesis were explored using different temperatures and various metal halides as additives. The most favorable conditions involved the use of 2.5 M NaOH, LiCl (0.1 equiv), and $NiCl_2.6H_2O$ at 40°C, or LiCl (0.1 equiv) at 50°C, resulting in a significantly reduced conversion time from 24 hours to 2-2.30 hours. The use of reflux techniques further decreases the reaction time; however, the isolation of the product remains challenging as it tends to form a sticky paste, complicating the purification process (Ruiz et al., 2020). Consequently, the presence of impurities or other similar compounds after the reaction requires further purifying steps, which makes the synthesis process generate more waste, which is time-consuming and inefficient. Therefore, there is a need for the development of green alternative, more efficient and environmentally friendly methods.

In recent years, the use of ionic liquids and microwave-assisted organic synthesis (MAOS) has emerged as a cutting-edge approach for efficient and environmentally friendly chemical synthesis. Ionic liquids, owing to their unique properties such as low volatility, low toxicity, high thermal stability, and ability to dissolve a wide range of substances, have been extensively studied as alternative solvents and catalysts for the synthesis of chalcone compounds resulting from the Claisen Schmidt condensation reaction in solventless reactions (Yadav & Wagh 2020). Furthermore, these liquids possess the ability of enhance the kinetic reaction rate and influence reaction pathways to increase reaction selectivity, minimizing the production of unwanted byproducts (Singh & Savoy 2020). On the other hand, microwave-assisted organic synthesis (MAOS) is recognized for significantly reducing reaction times and improving yields by providing rapid and uniform heating (Nayak, Devi & Vidyapeeth 2016).

This study reports the synthesis of chalcone derivatives from an aldol condensation reaction between benzaldehyde and acetophenone derivatives in imidazolium-based ionic liquid media such as 1-octyl-3-methylimidazolium bromide ([OMIM]Br), 1-decyl-3-methylimidazolium bromide [DMIM]Br, and 1-dodecyl-3-methylimidazolium bromide [DDMIM]Br, using the MAOS (microwave-assisted organic synthesis) method, which is an environmentally friendly alternative method with a shorter reaction time and produces a high yield percentage (Ain 2018; Pasha 2019; Santoso 2019; Sirait 2020; Auliawati 2021). While there has been significant research on the application of imidazolium-based ionic liquids and MAOSs in various Claisen-Schmidt reactions, there is a notable absence of studies specifically investigating the synthesis of DHZ via these combined methods. This research gap includes a lack of studies exploring the use of [DMIM]Br as a solvent and catalyst in the DHZ synthesis process and an absence of investigations into the combined effects of ionic liquids and microwave irradiation on the efficiency and selectivity of the reaction. By addressing these gaps, this study aims to provide new insights and potentially alternative methods for synthesizing DHZ.

The literature on the synthesis of DHZ has focused primarily on traditional methods, which often involve long reaction times, low yields, and the excess use of harmful organic solvents. This research introduces a novel approach to the synthesis of DHZ by combining the unique solvent and catalytic properties of ionic liquids with the efficiency of the MAOS method. In this research, a 1-decyl-3-methylimidazolium bromide ([DMIM]Br) ionic liquid was used. This research aims to study the effects of the use of the ionic liquid [DMIM]Br and the MAOS method on the resulting products of the synthesis of dehydrozingerone (DHZ).

METHOD

Materials

1-Methylimidazole p.a. (Sigma Aldrich), bromodecane p.a. (Sigma Aldrich), demineralized water, n-hexane p.a. (Merck), chloroform p.a. (Merck), methanol p.a. (Merck), dichloromethane p.a. (Merck), and ethyl acetate p.a. (Merck) for ionic liquid synthesis. The materials used for DHZ synthesis were vanillin (Merck), acetone p.a. (Merck), NaOH (Merck), demineralized water, synthesized ionic liquid [DMIM]Br, HCl

10% (Merck), dichloromethane p.a. (Merck), and ethyl acetate p.a. (Merck) for TLC.

Synthesis of the [DMIM]Br ionic liquid

1-Decyl-3-methylimidazolium ([DMIM]Br) was prepared via a domestic SHARP R-249 N(W) microwave oven following the method reported by Varma & Namboodiri (2001). 1-Methylimidazole (0.01 mol) and 1-bromodecane (0.01 mol) were added to a 50 mL beaker and then stirred for a few moments until homogeneous. After that, the mixture was heated in a microwave for a total of 25 s in 3 heating stages (10, 10, and 5 s). The [DMIM]Br was obtained as a yellow viscous liquid and then extracted with n-hexane: water (1:1) three times. The water phase of [DMIM]Br was then collected and vacuum distilled at a temperature of 180–210°C and a pressure of 38 cmHg to remove water and obtain a pure ionic liquid. The product in approximately 74,50% yield was then characterized by TLC and ^{1}H and ^{13}C NMR.

Synthesis of DHZ in the [DMIM]Br ionic liquid and the MAOS method

The synthesis of DHZ was carried out in [DMIM]Br ionic liquid medium and irradiated with Microwave CEM © Discover. First, 2 mL of 2.5 M NaOH was placed in a boiling flask, mixed with [DMIM]Br ionic liquid at different concentrations (1%, 3%, 5%, 7%, 10%, and 12% (w/v)) and then stirred to form a suspension. Then, acetone (30 mmol) was added, and the mixture was stirred to obtain a homogenous mixture. After that, vanillin (3 mmol) was added dropwise to form a yellow solution. The mixture was then irradiated via a CEM © Discover Microwave at 50°C and 200 W for 120 minutes. The reactions were monitored by thin layer chromatography (TLC) using dichloromethane:ethyl acetate (25:1, v/v) as the eluent. A red solution was obtained after the samples were exposed to microwave radiation. HCl (10%, v/v) and demineralized water were then added dropwise to the mixture while it was stirred over an ice bath until a yellow solid formed. The yellow solid that has formed is then filtered through a vacuum filter while being rinsed with distilled water. The yellow solid was then dried in an oven at 80°C, weighed, and characterized via TLC, melting point testing, and ^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR.

RESULTS AND DISCUSSION

Dehydrozingerone (DHZ) was obtained as a bright yellow solid with a yield of 62.95%. The characterization results of DHZ showed m.p. 129–130°; IR

(KBr, cm^{-1}) 3300 cm-1 (broad, OH), 3004 (C-H Ar), 2950, 2930, 2857 (C-H aliphatic), 1638 (α,β-unsaturated C=O), 1581, 1521 (C=C Ar), 968 (trans RC=CHR). ^{1}H-NMR ($CDCl_3$); □ ppm 2.35 (s, 3H), 3.90 (s, 3H), 6.24 (s(b), 1H), 6.57 (d, ^{3}J = 16.25 Hz, 1H), 6.92 (d, J = 8.15 Hz, 1H), 7.03 (d, J = 2.05 Hz, 1H), 7.06 (dd, J = 2.1 and 6.1 Hz, 1H), 7.43 (d, ^{3}J = 16.3 Hz, 1H). ^{13}C-NMR ($CDCl_3$); □ ppm 27.34, 56.03, 109.53, 115.00, 123.61, 124.98, 126.93, 144.00, 147.08, 148.48, 198.69.

In this section, we present and discuss the findings of our investigation into the green alternative synthesis method of dehydrozingerone (DHZ) utilizing a 1-decyl-3-methylimidazolium bromide ([DMIM]Br) ionic liquid as the solvent and catalyst and the microwave-assisted organic synthesis (MAOS) method. The primary objective was to evaluate the effects of the use of the [DMIM]Br and MAOS methods in terms of yield, purity, and reaction time compared with those of conventional methods.

Dehydrozingerone is synthesized from vanillin and acetone via a cross-aldol condensation reaction (*Claisen-Schmidt condensation*). The cross-aldol condensation reaction is a condensation reaction involving two different carbonyl compounds. In this study, vanillin and acetone were reacted at a molar ratio of 1:10. The addition of excess acetone was carried out to prevent further aldehyde (vanilin) self-condensation reactions (Nielsen & Houlihan, 2011) and to prevent evaporation of acetone when it reacted because of its fairly low boiling point (56°C) (Handayani, Arianingrum & Haryadi 2011).

The *Claisen–Schmidt* condensation reaction can take place in the presence of a weak base such as hydroxide or alkoxide, provided that one of the carbonyl reactants does not have α hydrogen. Sodium hydroxide was used in this study. The hydroxide will attract protons from the alpha carbon in acetone to form enolate ions. The formation of carbon–carbon bonds then occurs because of the nucleophilic attack of the enolate ion on the electrophilic carbon of the carbonyl group in vanillin. The final process that occurs is protonation and deprotonation by hydroxide ions to form unsaturated α, β ketone compounds, which are dehydrozingerones in this reaction (Solomon & Fryhe 2011). The proposed reaction mechanism for the DHZ synthesis reaction is presented in Figure 1.

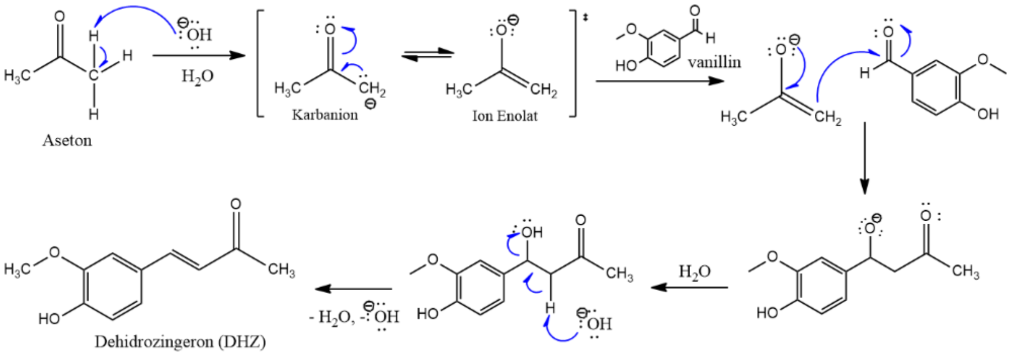

Figure 1. Proposed mechanism of the Claisen–Schmidt aldol condensation in dehydrozingerone (DHZ) synthesis

The conventional DHZ synthesis method involves the reaction of vanillin and acetone without the addition of [DMIM]Br ionic liquid at room temperature (25°C), which requires 48 hours of reaction time to produce a DHZ product in the form of a dark yellow solid with a melting point of 121-127°C and a yield percentage of 39.55%. Similar to the conventional synthesis method in previous studies by Abdelrahman (2017), 50% yield was obtained with a melting point 126–127°C, and Hayun (2018) reported a 33% yield with a melting point of 126–128°C.

In this study, DHZ was synthesized using [DMIM]Br ionic liquid at various concentrations to evaluate its effect on the DHZ synthesis process. The reactions were conducted at 50°C and 300 W using a CEM® Discovery microwave instrument for 3 hours. The reaction times for the synthesis of DHZ from vanillin and acetone are notably longer than those for the synthesis of chalcone from ortho-vanillin and acetophenone. This observation contrasts with previous studies conducted by Ain (2018), Pasha (2019), Santoso (2019), Sirait (2020), and Auliawati (2021), which reported that chalcone synthesis using MAOSs and ionic liquids could be completed in very short amounts of time (approximately minutes), whereas DHZ synthesis using MAOSs in this study requires approximately 2-3 hours. The prolonged reaction time for DHZ synthesis can be attributed to several factors related to the reactivity and structural differences between the reactans (Perin and Chang, 2016). DHZ synthesis involves the reaction between vanillin and acetone, which requires overcoming steric and electronic hindrances associated with vanillin substituents. Vanillin, which has a methoxy group at the para position and a hydroxyl group at the meta position, has a less reactive carbonyl group in the aldol condensation reaction because the steric and electronic effects of these substituents make the aldehyde group less accessible for nucleophilic attack. This results in a slower reaction due to less favorable conditions for the formation of the enolate ion. In contrast, chalcone synthesis with ortho-vanillin and acetophenone benefits from the increased reactivity of ortho-vanillin, with substituents at the ortho positions relative to the aldehyde group resulting in significantly different reactivity profiles, leading to faster product formation.

The reduction reaction times from 48 hours to 3 hours indicate that [DMIM]Br not only acts as a solvent but also as a catalyst in the aldol condensation. The 1-decyl-3-methylimidazole cation enhances the reactivity of vanillin's carbonyl group through ion–dipole interactions, accelerating the reaction. The proposed mechanism is illustrated in Figure 2. Molecules with weak proton donors/acceptors such as aromatic ketones, aliphatic ketones, aldehydes, and esters, interact with ionic liquids via induced ion–dipole interactions or weak van der Waals interactions (Wasserscheid & Welton 2008). In this regard, the 1-decyl-3-methylimidazole cation interacts ion-dipole with the O carbonyl in the vanillin compound, which is an aldehyde. This interaction causes the C carbonyl in vanillin to be more reactive so that the reaction can take place more quickly.

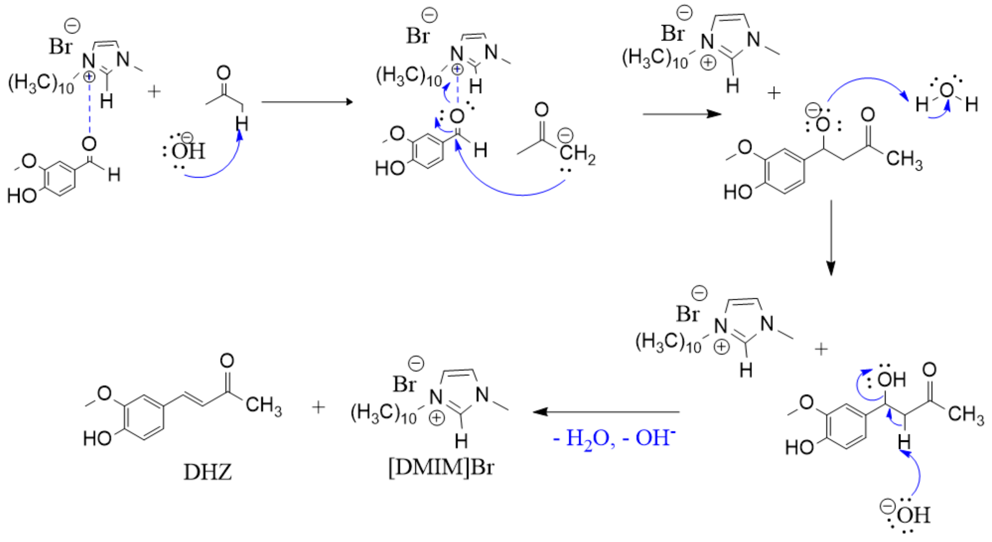

Figure 2. Proposed Claisen-Schmidt condensation reaction mechanism in DHZ synthesis catalyzed by the [DMIM]Br ionic liquid

Table 1. Experimental data for DHZ synthesis at various [DMIM]Br concentrations

No	Concentration [DMIM]Br (w/v)	Reaction time (hours)	Product color, melting point range	Yield Percentage (%)
1	1%	3	dark yellow, 120-126 °C	74.31
2	3%	3	dark yellow, 119-125 °C	62.46
3	5%	3	bright yellow, 129-130 °C	62.96
4	7%	2	bright yellow, 128-129 °C	60.90
5	10%	2.5	bright yellow, 129-131 °C	52.67
6	12%	3	bright yellow, 128-130 °C	48.63

Figure 3. DHZ synthesis products reacted in [DMIM]Br at various concentrations

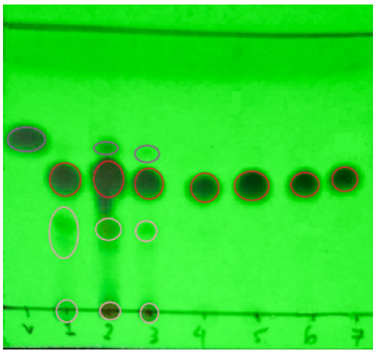

Figure 4. Thin layer chromatography (TLC) results of the vanillin and 7 DHZ products in DCM:ethyl acetate (25:1 (v/v)) eluent. Notes: V = vanillin, 1 = DHZ synthesis without [DMIM]Br, DHZ in [DMIM]Br 1%, 3 = DHZ in [DMIM]Br 3%, 4 = DHZ in [DMIM]Br 5%, 5 = DHZ in [DMIM]Br 7%, 6 = DHZ in [DMIM]Br 10%, 12 = DHZ in [DMIM]Br 12%.

The optimization data for DHZ synthesis in the [DMIM]Br ionic liquid medium via the MAOS method are presented in Table 1. Compared with that of the conventional method, the yield of DHZ increased with the addition of [DMIM]Br ionic liquid, ranging from 48.63% to 74.31%. Although the highest yield was obtained with the 1% (w/v) ionic mixture, TLC analysis revealed impurities in the product. The best yield of pure DHZ, 62.96%, was achieved with 5% (w/v) [DMIM]Br. The physical appearance of the synthesized DHZ is shown in Figure 3.

One interesting finding from this research is the variation in the color of DHZ products synthesized with different concentrations of the [DMIM]Br ionic liquid. The products synthesized without ionic liquid or with up to 3% (w/v) [DMIM]Br were dark yellow solids, whereas those synthesized with 5% to 12% [DMIM]Br were bright yellow. The thin layer chromatography (TLC) analysis shown in Figure 4 using DCM:ethyl acetate (25:1, v/v) as the eluent revealed that DHZ samples synthesized with 5%-12% [DMIM]Br produced a single spot with an Rf value of 0.47, indicating purity. In contrast, samples synthesized without an ionic liquid or with up to 3% [DMIM]Br displayed additional spots, indicating impurities. Product identification involves melting point testing to assess purity, where a large melting point range (>2°C) indicates impurities (Nichols, 2017). The results obtained in this study align closely with those of previous research by Formentin (2004), who also reported the ability of imidazolium ionic liquids to increase selectivity for base-catalyzed reactions such as the Knoevenagel and Claisen-Schmidt reactions.

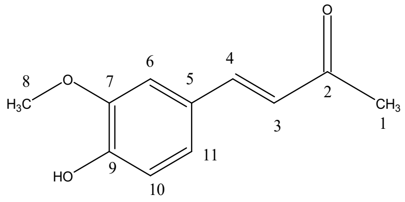

Figure 5. Structure of dehydrozingerone (DHZ)

The structural representation of DHZ is presented in Figure 5. The structural identity of the bright yellow product obtained from the synthesis was confirmed through comprehensive analysis via Fourier transform infrared (FTIR) spectroscopy and ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy. The FTIR spectrum provided key functional group information, whereas the NMR spectra confirmed the presence and arrangement of hydrogen and carbon atoms, respectively. The data obtained were consistent with those reported by Kubra et al. (2014), validating the identity of the compound as dehydrozingerone (DHZ).

CONCLUSION

Dehydrozingerone (DHZ) was successfully synthesized from vanillin and acetone in a [DMIM]Br ionic liquid medium via the microwave-assisted organic synthesis (MAOS) method with a CEM® Discovery microwave instrument at 50°C for 3 hours. These results indicate that the addition of the [DMIM]Br ionic liquid significantly affects the purity and yield of the DHZ product. The optimal conditions resulted in a bright yellow solid with a melting point of 129–130°C and a yield of 62.96% when 5% (w/v) [DMIM]Br was used. This study demonstrates the potential of combining ionic liquids and MAOS for alternative efficient and environmentally friendly DHZ synthesis, offering a reduction in reaction time and energy consumption while minimizing the use of harmful organic solvents. The implications of this research are notable for the advancement of green chemistry and the enhancement of DHZ and Claisen-Schmidt chemical synthesis efficiency, offering valuable insights for both educational purposes and practical applications in green synthesis techniques. However, this research has certain limitations that need to be addressed in future studies. The specificity of this study to the [DMIM]Br ionic liquid suggests the potential for exploring other types of ionic liquids to achieve better yields and efficiencies. It is also recommended that computational studies be conducted to predict synthesis outcomes, minimizing the need for extensive experimental trials and making the synthesis process more efficient. Further research should include bioactivity testing of DHZ to evaluate its potential therapeutic benefits.

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