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SYNTHESIS OF DIBENZALACETONE USING SONOCHEMISTRY AND ITS ANTIBACTERIAL ACTIVITY AGAINST *Escherichia coli*

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ABSTRACT

The synthesis of dibenzalacetone, a ketone compound with potential antibacterial properties, especially against *Escherichia coli*, has typically involved time-consuming methods. This study adopts sonochemistry, an increasingly popular technique recognized for its efficiency and quick yield. The aim is to synthesize dibenzalacetone using the sonochemical method and evaluate its antibacterial efficacy against *E. coli*. The synthesis process includes a cross-aldol condensation reaction between acetone and benzaldehyde, catalyzed by NaOH, conducted in an ultrasonic bath at 35 °C for 1-5 minutes. The optimal synthesis condition, achieved in 4 minutes, resulted in a 76.56% yield of dibenzalacetone, characterized as a bright yellow solid with a melting point of 111-114°C. Techniques such as FT-IR, GC-MS, 1H-NMR, and 13C-NMR spectrometry were employed for structural characterization. The FTIR analysis revealed various functional groups, including C=O ketone, C=C aromatic, and C-H aromatic. GC-MS data confirmed the molecular weight of dibenzalacetone at m/z 234.1. Furthermore, ^{1}H-NMR and ^{13}C-NMR analyses provided detailed insights into the compound's chemical shifts and structural groups, affirming the successful synthesis of dibenzalacetone. The antibacterial activity of dibenzalacetone against *E. coli* was tested at concentrations ranging from 5% to 20%. Notably, at a 15% concentration, dibenzalacetone exhibited antibacterial activity comparable to amoxicillin. These findings suggest that dibenzalacetone, efficiently synthesized via sonochemistry, achieves a high yield and has potential as an antibacterial agent against *E. coli*. This research highlights the efficacy of sonochemistry for the rapid and effective synthesis of compounds with significant medical applications.

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INTRODUCTION

The escalating issue of antimicrobial resistance (AMR) has emerged as a paramount public health concern in the 21st century, posing a serious threat to the effectiveness of conventional treatment strategies against a broad range of infections. These infections, caused by bacteria, parasites, viruses, and fungi, have increasingly become resistant to standard medicinal treatments [1]. The phenomenon of antimicrobial resistance was first observed in the late 1950s and early 1960s, particularly in intestinal bacteria such as *E. coli, Shigella*, and *Salmonella*. These resistant strains have led to significant clinical challenges and elevated mortality rates, especially in underdeveloped nations. In the early stages, more developed countries perceived this resistance as a minor issue, limited to gastrointestinal organisms in remote locations [2].

However, over time, the problem of bacterial infections resistant to multiple

Antibiotics have evolved into a grave global health emergency. Despite developing various strategies in the last decade to tackle these infections, the emergence of bacterial pathogens resistant to numerous antibiotics continues to be a considerable public health issue. This alarming situation highlights the critical need to discover and develop new antimicrobial agents [3]. In this context, amino ketones have gained attention as potentially effective antibacterial compounds [4]. Certain ketones have demonstrated antibacterial effectiveness against a range of pathogens, including *E. coli* [5], *Staphylococcus aureus* [6], and *Bacillus subtilis* [7]. Notably, dibenzalacetone, a ketone compound widely utilized in cosmetic sunscreens [8], has also been identified for its antioxidant [9] and antileishmanial activities [10]. This evolving understanding of the antibacterial properties of ketones, including dibenzalacetone, opens new avenues in the quest for effective treatments against AMR, underlining the necessity of ongoing research and development in this crucial field of public health.

In organic synthesis, the conventional preparation of dibenzalacetone typically employs a cross-aldol condensation reaction between acetone and benzaldehyde, facilitated by sodium hydroxide (NaOH) as a catalyst [10]. Conventional methodologies, such as the grinding technique, although rapid, yielding approximately 53% of the product within a mere 2-minute duration [11], do not epitomize efficiency in terms of overall yield. Furthermore, alternative methods that utilize a NaOH/ZrO_2-montmorillonite catalyst extend the reaction duration considerably, up to 4 hours at a temperature of 10 °C, yet yield less than 50% [12]. These shortcomings in the traditional synthesis approaches underscore an exigent need for more advanced, efficient synthesis techniques.

Sonochemistry, emerging as a formidable alternative within green synthesis, is lauded for its simplicity, efficiency, and high yield capacity. Its notable attributes include cost-effectiveness, rapid reaction kinetics, and environmentally benign nature [13]. This technique has demonstrated its versatility and efficacy across a spectrum of chemical reactions [14], encompassing esterification [15-17], amide synthesis [18], and aldol condensations [19,20], thereby establishing its utility in contemporary organic synthesis.

In light of these attributes, the current research explores the sonochemical synthesis of dibenzalacetone. The objective is to evaluate the sonochemical method's efficiency in synthesizing dibenzalacetone, particularly focusing on yield optimization and reaction time reduction. Concurrently, the study aims to investigate the antibacterial efficacy of dibenzalacetone against *Escherichia coli*. This investigation is poised to contribute significantly to the field of antimicrobial research, particularly in combating antimicrobial resistance. Should the sonochemical approach prove successful, it could signify a paradigm shift in the rapid, sustainable synthesis of medically pertinent compounds.

METHODS

1. Material and Instrument

The synthesis of dibenzalacetone utilized reagents and solvents of synthesis or pro-analysis grade, specifically benzaldehyde, acetone, sodium hydroxide (NaOH), ethanol, hexane, and ethyl acetate, all procured from Sigma Aldrich. For the antibacterial test, *Escherichia coli* ATCC 8739 was employed.

The sonochemical synthesis was conducted using a Bransonic Ultrasonic Bath series CPX1800H operating at 40 kHz.

The characterization of the synthesized compound involved several analytical techniques. The infrared spectrum was recorded using ATR-FTIR (Agilent Technology, model 630) at the Semarang Pharmaceutical College. The melting point of dibenzalacetone was determined using an electrothermal melting point apparatus. Nuclear Magnetic Resonance (NMR) spectroscopy and Gas Chromatography-Mass Spectrometry (GCMS) analyses were performed at the LPPT, Gajah Mada University. The instrument specifications included a ^{1}H-NMR spectrometer (JEOL JNM-ECA500 operating at 500 MHz) and a ^{13}C-NMR spectrometer (JEOL, JNM-ECZ500R operating at 500 MHz). GCMS analysis was conducted using an HP-5MS UI column. These analytical methods were critical in determining the structural and chemical properties of the synthesized dibenzalacetone, ensuring its purity and confirming its identity

2. Synthesis of dibenzalacetone

The methodology for this synthesis was adapted and modified from a previously established protocol [10]. Initially, 0.0198 moles of benzaldehyde were combined with 0.136 moles of acetone and allowed to stand at room temperature for 5 minutes. This mixture was then transferred to an Erlenmeyer flask containing an ethanolic NaOH solution (prepared by mixing 20 mL of 10% NaOH with 15 mL of 95% ethanol and subsequently cooled). The resultant solution was subjected to sonication at 35 °C for varying durations ranging from 1 to 5 minutes, with each duration repeated twice. The precipitate formed was filtered and then recrystallized using ethanol as the solvent. The recrystallized product was dried in a drying oven at 60 °C.

3. Synthetic characterization

The precipitate obtained from the synthesis process was subjected to a melting point test using a melting point apparatus and monitored through Thin Layer Chromatography (TLC) using a hexane: ethyl acetate (9:1) eluent, which revealed a single spot. The synthesized compound's structure was further characterized using Fourier Transform Infrared Spectroscopy (FT-IR), Gas Chromatography-Mass Spectrometry (GC-MS), Proton Nuclear Magnetic Resonance (^{1}H-NMR), and Carbon-13 Nuclear Magnetic Resonance (^{13}C-NMR).

4. Antibacterial Test

The antibacterial activity was evaluated using a modified standard method [21]. Nutrient Agar media was melted at 45 °C and poured (15 mL) into sterile Petri dishes, which were left to solidify. Six-cylinder cups were placed on the solidified media. An *E. coli* suspension, adjusted to the turbidity of the McFarland standard, was pipetted (100 µl) into an Erlenmeyer flask containing 5 ml of nutrient agar, mixed thoroughly, and then poured aseptically into sterile Petri dishes. The mixture was spread evenly and allowed to solidify. Subsequently, the cylinder cups were removed, and wells were created to add 20 µl of the test preparation at concentrations of 5%, 10%, 15%, and 20%. Amoxicillin and DMSO served as positive and negative controls, respectively. The process was replicated three times. Incubation occurred at 24 °C for 24 hours, after which the diameter of the clear zones around the test solution was measured using a caliper [22,23].

RESULTS AND DISCUSSION

1. Synthesis of dibenzalacetone: Mechanism and Reaction Conditions

The synthesis of dibenzalacetone is typically achieved through a cross-aldol condensation reaction, a specific type known as the Claisen-Schmidt reaction involving acetone and benzaldehyde. In this reaction, acetone, possessing alpha hydrogen atoms, reacts with benzaldehyde, which lacks these alpha hydrogens. The key to this process is the use of an ethanolic base catalyst. Here, ethanol is reacted with sodium hydroxide (NaOH) to form sodium ethoxide, a potent base.

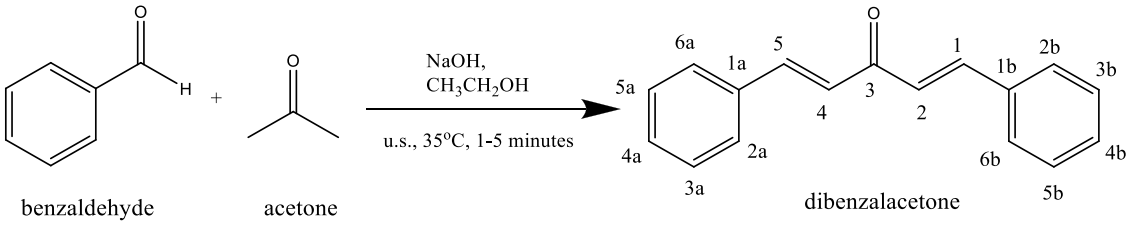

Figure 1. Dibenzalacetone synthesis reaction.

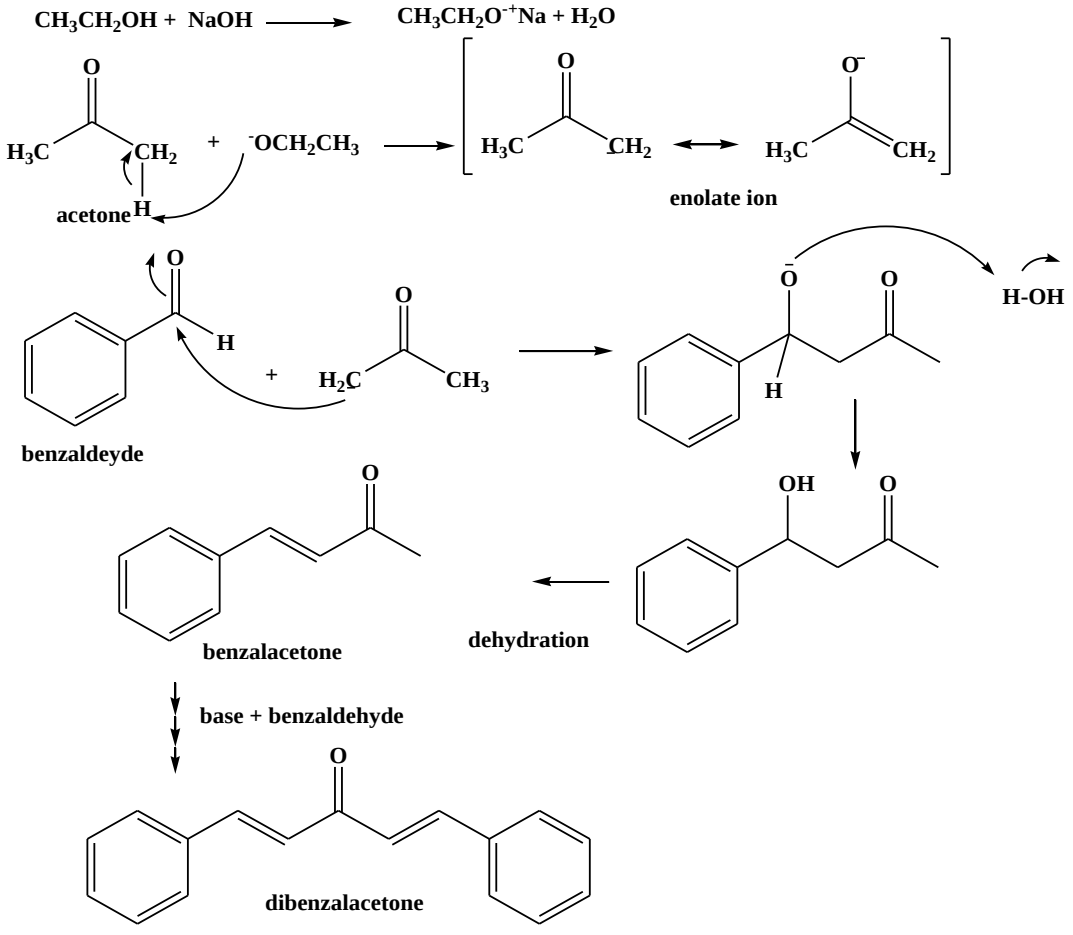

Figure 2. The reaction mechanism for the formation of dibenzalacetone.

The sodium ethoxide acts on the acetone, binding to its acidic alpha hydrogen to create an enolate ion. This enolate ion is nucleophilic, meaning it has a propensity to donate a pair of electrons. This nucleophilic character enables the enolate ion to attack the carbonyl group of the benzaldehyde. The initial

product of this nucleophilic attack is an aldol, a beta-hydroxy ketone, or beta-hydroxy aldehyde.

Subsequently, this aldol undergoes a dehydration reaction involving removing a water molecule. This dehydration leads to the formation of dibenzalacetone. The reaction pathway effectively combines the carbonyl group of benzaldehyde with the enolate ion derived from acetone, resulting in the formation of dibenzalacetone, characterized by its conjugated enone structure. This process highlights the utility of cross-aldol condensation reactions in synthesizing complex organic molecules from simpler precursors, with the ethanolic base playing a crucial role in facilitating the reaction (Figure 1).

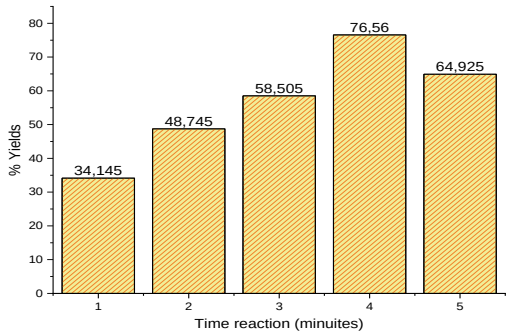

Figure 3. The results of the synthesis of dibenzalacetone with time variations.

The synthesis was carried out with the help of ultrasonic waves in a simple sonicator bath at a frequency of 40 Hz. This synthesis was carried out with five variations of time, namely 1–5 minutes, to see the optimum time at 35 °C. Ultrasonic irradiation can increase the reaction between benzaldehyde and acetone through a cavitation mechanism. This irradiation produces microfine bubbles at the phase boundary. The cavitation bubbles will eventually collapse to disrupt the phase boundary, creating micro-jets so that the system's mixing becomes intensive near the phase boundary [24]. Cavitation can also cause an increase in the local temperature at the phase boundary, thereby increasing the condensation reaction between benzaldehyde and acetone and forming dibenzalacetone in the form of a yellow solid.

Based on Figure 3, the % yield of dibenzalacetone in this study increased from the synthesis time of 1 minute to 4 minutes, with the % yield respectively 34.15%, 48.75%, 58.51%, and 76.56%. However, within 5 minutes, the resulting dibenzalacetone decreased to 64.93%. It shows that the optimal time to produce dibenzalacetone maximal is 4 minutes. The increase in % yield from 1 minute to 4 minutes was due to the longer the sonication process, the more cavitation bubbles formed and caused a shockwave. Cavitation and shockwaves can move particles faster. Collisions between the resulting particles cause the reaction to occur more quickly and altogether [25]. The addition of time causes the mixture to become saturated. It shows that the sonochemically synthesized mixture has an energy limit. When this energy limit is crossed, the chemical reaction that takes place is reduced so that the formation of the synthesis product decreases [26]. It happens when the time is added to 5 minutes, so the % yield decreases.

Table 1. Melting point of dibenzalacetone

Reaction time(minutes)	Replication	Melting point (°C)
1	1.1	110 – 112
	1.2	111 – 114
2	2.1	110 – 114
	2.2	109 – 114
3	3.1	109 – 113
	3.2	110 – 112
4	4.1	111 – 114
	4.2	111 – 113
5	5.1	108 – 111
	5.2	109 – 113

Monitoring the synthesis results using TLC with mixed eluent n-hexane: ethyl acetate (9:1) showed a single stain with Rf 0.44. It

indicates that the synthesized compound is pure. This data is also supported by the synthesized compound melting point, which shows a 2–5 °C melting point range. The melting point of the synthesized compounds ranged from 108–114 °C (Table 1). It shows that the synthesized compound is dibenzalacetone according to the melting point of dibenzalacetone from literature, including 108.8–113 °C [8,10,27].

2. Elucidation structure

The synthesis results of dibenzalacetone were monitored using thin-layer chromatography (TLC) with a mixed eluent of n-hexane and ethyl acetate in a 9:1 ratio. The TLC analysis revealed a single spot with an Rf (Retention factor) value of 0.44, suggesting the purity of the synthesized compound. This observation is a crucial indicator in qualitative analysis, as a single spot on the TLC plate generally implies the absence of impurities or by-products in the synthesized sample. Additionally, the purity of the synthesized dibenzalacetone was further corroborated by its melting point analysis. The melting point range observed for the compound was between 108-114 °C, as listed in Table 1. This melting point range is consistent with the reported melting point of dibenzalacetone in the literature, which varies between 108.8–113 °C [8,10,27]. The agreement of the experimental melting point data with the literature values substantiates the identity of the synthesized compound as dibenzalacetone. The congruence of the melting point data with the established literature values, combined with the TLC results, strongly supports the successful synthesis and purity of dibenzalacetone. Such consistency is vital in synthetic chemistry to confirm that the intended compound has been synthesized and is free from significant impurities.

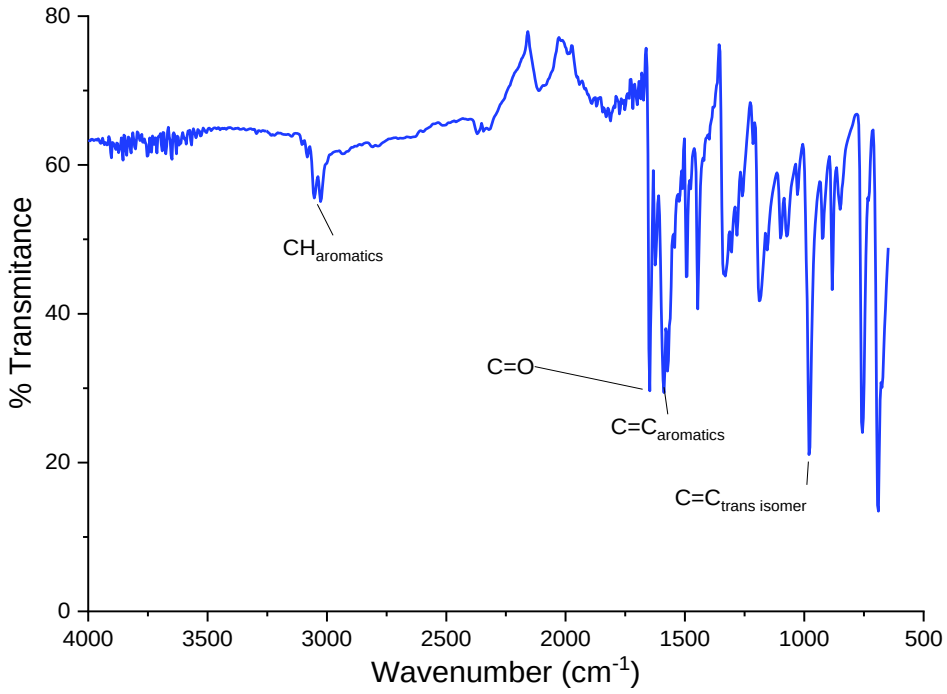

Figure 4. FTIR spectrum of dibenzalacetone.

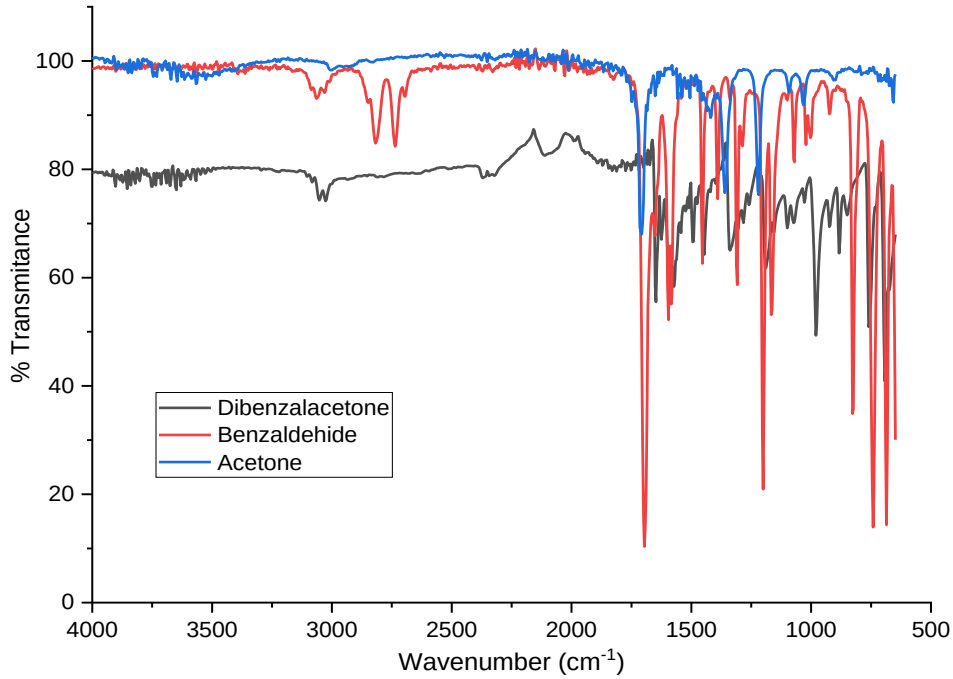

Figure 5. Overlay FTIR spectrum of benzaldehyde, acetone, and benzal acetone.

Based on the overlay spectrum (Figure 5) between the synthesis product and its precursors, it can be seen that the synthesis results show a slightly different spectrum profile from the precursors. The synthesized compound had no aldehyde C-H group at 2817 and 2735 cm^{-1}. The C=O group in the synthesized compound is also slightly different in absorption compared to its constituent acetone. Because the synthesized compound is influenced by the group attached to the side chain of the C=O, there is a slight shift in the wavenumber. In addition, the resonance effect with the C=C bond causes the delocalization of pi electrons in both groups, so it will decrease the double bond character of C=O, which causes a decrease in absorption.

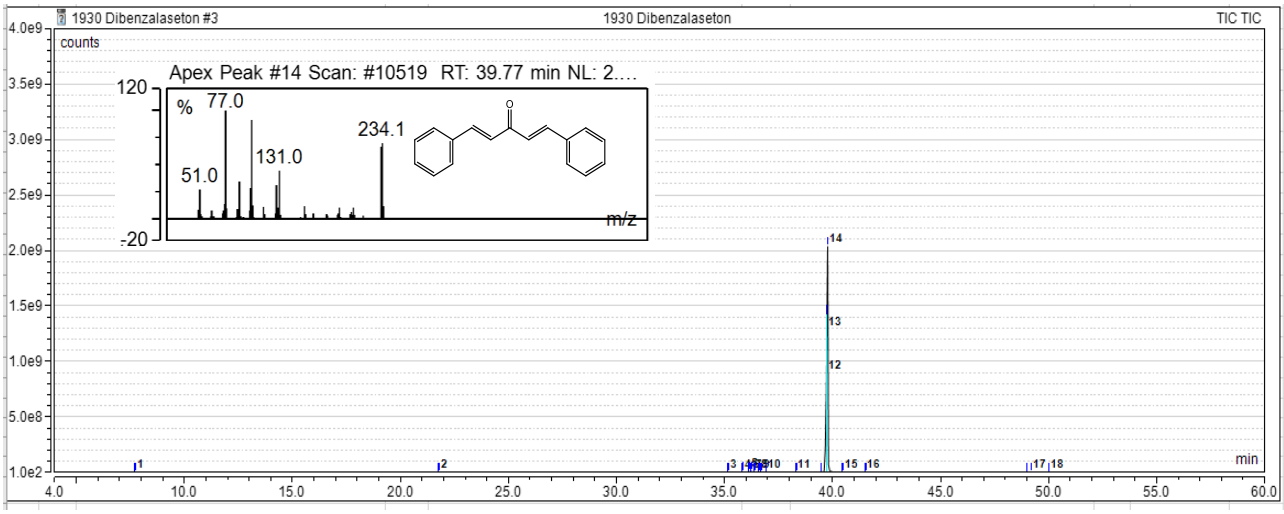

Figure 6. The GC-MS of dibenzalacetone.

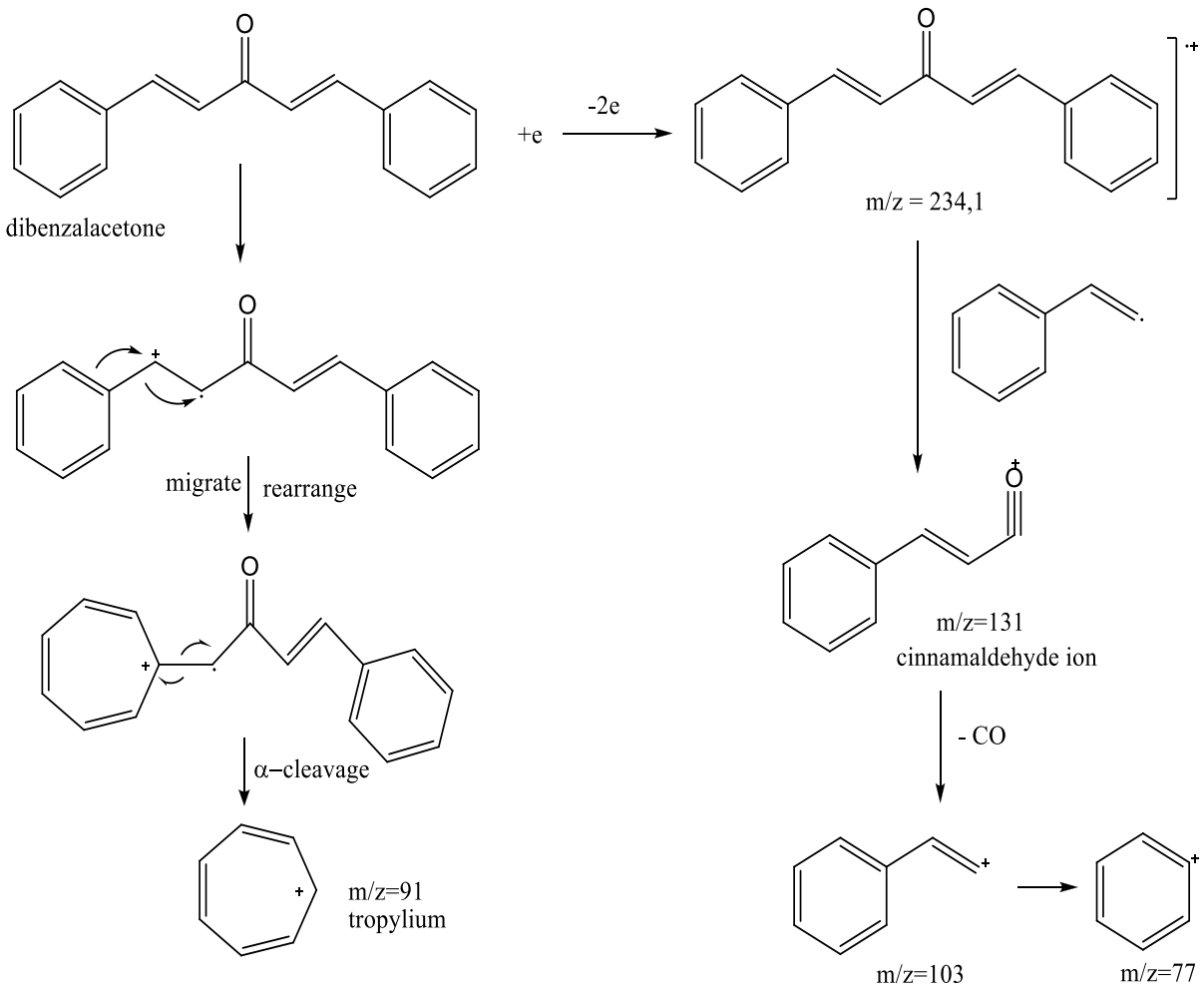

Figure 7. Fragmentation mass spectra of dibenzalacetone.

Table 2. Data of ^{1}H-NMR and ^{13}C-NMR dibenzalacetone

C Position	δ_C (ppm)	δ_C (ppm) [29]	δ_H (ppm) (∑H, multiplicity, J (Hz)	δ_H (ppm) (∑H, multiplicity, J (Hz) [29]
1	145.281	143.7	7.806 (2H, d, 16)	7.78 (2H, d, 15.4)
2	126.506	124.8	7.276 (2H, d, 16)	7.10 (2H, d, 15.4)
3	191.547	189.4	-	-
4	126.506	124.8	7.276 (2H, d, 16)	7.10 (2H, d, 15.4)
5	145.281	143.7	7.806 (2H, d, 16)	7.78(2H, d, 15.4)
1a, 1b	136.364	134.2	-	-
2a, 6a, 2b, 6b	129.818	128.8	7.718 (4H, m, 3.5)	7.60 (10H, m)
3a, 5a, 3b, 5b	130.221	129.3	7.424 (4 H, m, 2.5)	7.52 (10H, m)
4a, 4b	131.910	130.5	7.704 (2H, d, 2)	7.52–7.6 (10H, m)

In the conducted Gas Chromatography-Mass Spectrometry (GC-MS) analysis, as delineated in Figures 6 and 7, dibenzalacetone was identified with a retention time of approximately 39.72 to 39.77 minutes, exhibiting a peak representing an abundance of

97.85%. This peak corresponded to a mass-to-charge ratio (m/z) of 234.1 [10], which is indicative of the molecular mass of dibenzalacetone.

The mass spectrometric analysis elucidated several distinct m/z values, signifying various fragment ions. The fragment ion at m/z 131 suggests cinnamaldehyde ions forming from bond cleavage at the alpha position adjacent to the carbonyl group. Additionally, the emergence of a fragment ion at m/z 103 denotes the presence of styrene ions, likely resulting from bond breakage at the beta position relative to the carbonyl group.

The mass spectrum peaked at m/z 91, aligning with the presence of tropylium ions [8]. The fragment ion observed at m/z 77 indicates phenyl groups, while the peak at m/z 51 correlates with the presence of $C_4H_3^+$ ions. The fragmentation pattern elucidated in the GC-MS spectrum is consistent with the chemical structure of dibenzalacetone, affirming its synthesis with a molecular mass of 234.1 g/mol [27]. This comprehensive analysis via GC-MS not only substantiates the successful synthesis of dibenzalacetone but also provides a detailed insight into its molecular structure and fragmentation pathways.

The nuclear magnetic resonance (NMR) spectroscopy results for the synthesized dibenzalacetone were consistent with its expected chemical structure, as detailed in Table 2. Both ^{1}H-NMR and ^{13}C-NMR spectra were recorded using deuterated methanol (CD3OD) as the solvent at a frequency of 500 MHz.

In the ^{1}H-NMR spectrum, several distinctive absorptions were observed in the 7.0–8.0 ppm. Owing to the symmetrical nature of the dibenzalacetone molecule, the spectrum exhibited only five peaks, each corresponding to different atomic positions within the structure. Specifically, a chemical shift at 7.086 ppm indicated the presence of two hydrogen atoms, appearing as a simple doublet associated with H atoms at C1 and C5. The proton at C1 exhibited a trans configuration relative to C2, while C5 was trans to C4. A chemical shift at 7.726 ppm corresponded to the hydrogen atoms at C2 and C4, which are trans to C1 and C5, as evidenced by a coupling constant of 16 Hz. Additionally, the chemical shift at 7.718 ppm represented the hydrogen atoms at C2a and C6a and C2b and C6b, which are in meta positions to each other, indicated by a coupling constant of 3.5 Hz. The shift at 7.424 ppm suggested the location of hydrogen atoms at C3a and C5a, and C3b and 5b, which are also meta to each other, with a coupling constant of 2.5 Hz.

In the ^{13}C-NMR spectrum, several peaks were observed, each correlating to different types of carbon atoms within the dibenzalacetone structure. A chemical shift at 191.547 ppm indicated a carbonyl group (C=O ketone) [30]. The shift at 145.281 ppm denoted a carbon (C) atom in an alkene bond linked to an aromatic ring. A shift at 126.506 ppm was attributed to a carbon atom in the alkene group bonded to the carbonyl group. Finally, shifts at 136.364, 129.818, 130.221, and 131.910 ppm were characteristic of carbon atoms within the aromatic ring, confirming the aromatic nature of the synthesized dibenzalacetone.

3. Antibacterial activity of dibenzalacetone against *E. Coli*

The antibacterial activity of dibenzalacetone was assessed by measuring the diameter of the inhibition zone, which represents the largest clear area formed around

the well, indicative of bacterial growth inhibition [31,32]. In this experiment, dibenzalacetone was tested against *Escherichia coli* (*E. coli*) at various concentrations: 5%, 10%, 15%, and 20%, with Amoxicillin at a concentration of 50 mg/L used as a positive control.

Figure 8. Antibacterial activity of dibenzalacetone at concentrations (A: 5%, B: 10%, C: 15%, D: 20%, E: DMSO negative control, and F: Amoxicillin 50 mg/L.

As depicted in Table 3, the results demonstrate that dibenzalacetone exhibits a considerable antibacterial effect at a concentration of 5%, with an increase in the inhibition zone corresponding to higher compound concentrations. This trend suggests an escalation in the antibacterial efficacy of dibenzalacetone with increasing concentration. The formation of inhibition zones in the presence of *E. coli* underscores the ability of dibenzalacetone to inhibit the growth of gram-negative bacteria. This feat can be challenging for some chemical compounds. The effectiveness of dibenzalacetone in inhibiting the growth of *E. coli* points to its potential as an antibacterial agent, particularly against gram-negative bacteria, which are often more resistant to certain types of chemical compounds. These findings highlight the prospective use of dibenzalacetone in developing new antibacterial treatments or preventive strategies, especially for infections caused by gram-negative bacteria like *E. coli.*

Table 3. Antibacterial activity test of Dibenzalacetone against *E. Coli*

Replication	Inhibition zone of dibenzalacetone (mm)				Control(+) (mm)	Control(-) (mm)
	5%	10%	15%	20%		
1	1.764	1.856	2.010	2.072	1.988	0.000
2	1.760	1.856	2.010	2.072	1.986	0.000
3	1.764	1.856	2.012	2.072	1.986	0.000
Average	**1.762**	**1.856**	**2.011**	**2.072**	**1.987**	**0.000**

At a concentration of 15%, the compound's ability was comparable to the antibiotic amoxicillin. The cell wall that is most easily denatured is a cell wall composed of polysaccharides compared to a cell wall composed of phospholipids. Gram-negative bacteria have three layers: lipopolysaccharide, protein, and hydrophobic phospholipids [33]. Dibenzalacetone compound has hydrophobic properties based on its solubility, so it will easily penetrate bacterial cell walls due to the same solubility properties and potential as bactericidal.

CONCLUSION

The findings from this research lead to several key conclusions regarding the synthesis and potential applications of dibenzalacetone. The compound can be successfully synthesized through a cross-aldol condensation reaction between acetone and benzaldehyde, utilizing sonochemistry as the synthesis method. An optimal synthesis time of 4 minutes was identified, resulting in a significant yield of 76.56%. This outcome underscores the efficacy of sonochemistry in facilitating a high yield within a remarkably short reaction duration. Additionally, the research indicates that dibenzalacetone possesses potential antibacterial properties against *Escherichia coli* (*E. coli*). The ability of dibenzalacetone to inhibit the growth of this gram-negative bacterium suggests its utility in developing antibacterial treatments or agents. This finding is particularly relevant given the increasing concerns about antibiotic resistance and the need for new antimicrobial compounds. The study demonstrates that sonochemistry offers an efficient and rapid method for synthesizing dibenzalacetone, yielding a compound that can be produced in a time-effective manner and shows promise as an antibacterial agent against *E. coli*. This research contributes valuable insights into organic synthesis and antimicrobial studies, potentially guiding future efforts in developing effective antibacterial agents.

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