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CONVENTIONAL AND MICROWAVE-ASSISTED SYNTHESIS OF 4'-BROMOCHALCHONE UTILIZING 4-BROMOACETOPHENONE AND BENZALDEHYDE AS STARTING MATERIAL IN ALKALINE CONDITION

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ABSTRACT

This study focuses on synthesizing 4'-bromochalcone through conventional and irradiation microwave methods to determine each method's time efficiency and yield. 4-Bromoacetophenone was treated with benzaldehyde in the presence of a base. Conventionally, the reaction mixture was stirred at room temperature. While in the microwave irradiation method, the reaction mixture was irradiated at a power of 140 watts. The compound was identified, including the melting point and physicochemical properties. The structure of the compound was confirmed by infrared, ^{1}H- and ^{13}C-nuclear magnetic resonance, and mass spectroscopy spectral data. The results showed that 4'-bromochalcone had been successfully synthesized using conventional and microwave irradiation methods in a good yield (94.61%±0.6793 and 89.39%±0.6418, consecutively). The structure assignment based on infrared, ^{1}H- and ^{13}C-nuclear magnetic resonance, and mass spectroscopy spectral data revealed that the synthesized product was 4'-bromochalcone. Synthesis of 4'-bromochalchone using microwave irradiation could be done in a shorter time than the conventional method.

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Keywords: *4'-bromochalcone, conventional method, irradiation microwave*

INTRODUCTION

Microwave-assisted organic synthesis has been applied to organic reactions [1]. It becomes an environmental-friendly method to synthesize organic compounds due to the absence and less hazardous solvent used in its application [2]. Conventionally, organic reactions that could not undergo or take longer at room temperature due to the high activation energy required have been conducted through conductive heating with external heat sources. On the laboratory scale, a hotplate stirrer equipped with an oil or water bath is commonly used as an external heat source, while the reaction mixture is placed in a round-bottom flask or a vessel. In this case, the transfer of energy from the heat sources into the reaction mixture becomes slow and inefficient. Moreover, the energy transfer also depends on the thermal conductivity of the round-bottom flask or the vessel used. Some studies have reported that microwave-assisted heating might become an alternative heating chemical reaction [3, 4].

In the microwave-irradiated process, the chemical reaction depends on the ability of the reagents in the reaction mixture to transform electromagnetic energy into heat [4]. Several advantages can be obtained by performing organic reactions using microwave irradiation, including rapid and selective heating and acceleration in the reaction process. Moreover, microwave-assisted organic synthesis enhances the yield of the product, reduces the number of impurities, and in some cases, gives a good selectivity [4]. Shah and Mahanraj have reported the comparison of conventional and microwave-assisted synthesis in organic synthesis applications. Their result indicated that in a short time, microwave-assisted synthesis (3 to 6 minutes 30 s) gave a higher yield than conventional (3 to 6 hours) [5].

Chalcones are widely known as α-β-unsaturated ketones. It is abundant in fruits and vegetables. It is commonly used as a core skeleton in the design and development of drug candidates. Generally, the preparation of chalcones is usually achieved by aldol condensation in acid or base conditions. Although aldol condensation reactions are rarely carried out in acid conditions, catalysts such as sulfuric acid in acetic acid [6] or thionyl chloride in absolute ethanol [7] can be used in this reaction. While in alkaline conditions, NaOH [8, 9] and KOH [10, 11] are commonly used as catalysts. Numerous studies have reported the preparation of chalcones by utilizing different types of catalysts. Modified graphene [12], CaAl-hydrotalcite [13], Zn–Al hydrotalcite [14], zink oxide [15], modified Al-silica mesoporous [16], and $NaNO_3$/NP [17] have been reported in the preparation of chalcones analogs.

For many years, chalcones have been investigated as an essential and emerging scaffold in drug development. In addition, it forms a significant component of the natural product and becomes a pharmaceutically pivotal precursor in the synthetic manipulation of bioactive compounds. Chalcone derivatives bearing five-membered N-heterocycles such as benzimidazole and imidazole, have been reported as monoamine oxidase A (MAO-A) and monoamine oxidase B (MAO-B) inhibitors [18]. N- substituted indolyl chalcones showed a broad potency as an anticancer, anti-inflammatory, and antioxidant agent [9]. Other studies reported that chalcones and their derivatives have several therapeutic activities, such as anti-microbial [19], anticancer [20], antitubercular [21], anti-leishmanial [22], and antidiabetic [23]. Recently, it has been reported by [24] that bromo and nitro chalcones have potency as schistosomicidal agents.

Due to their potential pharmacological activity and prominent structural diversity, chalcones and their derivatives could serve as a lead compound for developing other promising compounds/molecules. Therefore an effort to synthesize chalcones and their derivatives that give a better yield in short periods will be highly advantageous. Notably, in the present study, it has been contemplated worthwhile to synthesize chalcone derivatives employing microwave irradiation due to efficiency, convenience, better yield, and acceleration in the reaction process.

METHODS

Material and apparatus

The material used is Benzaldehyde, NaOH, ethanol, 4-bromoacetophenone, aquadest, *n*-hexane, ethyl acetate, and silica gel F 254. All chemicals were reagent grade, commercially available, and were directly used without any other purification unless otherwise mentioned. The melting point of the product was measured using Melting Point Apparatus. The microwave irradiation method was performed using a domestic microwave (LG Type MS2041C). TLC was accomplished on a TLC plate (silica gel 60 F_{254} (Merck-Millipore)). The spot on the TLC was visualized under ultraviolet light at 254 nm. FTIR analysis was performed using Shimadzu FTIR 8201 PC. The retention time of the product was determined using GC-MS (Shimadzu QP-2010 SE) with the following condition: injector temperature = 280 °C, column = Rtx-5MS, column length = 30 cm, carrier gas = helium, pressure = 85.6 kPa, and flow rate of carrier gas = 1.15 mL/min. ^{1}H-NMR and ^{13}C-NMR were accomplished using Agilent DD2 operating at 500 and 125 MHz rspectively. Acetone-*d6* was used as a deuterated solvent, while chemical shifts (δ) are expressed in part per million (ppm). The constant coupling values (*J*) are reported in Hertz (Hz).

Synthesis of 4'-bromochalcone using the conventional method (Method A)

4'-Bromochalcone was synthesized using a conventional method according to procedure literature reported by Chithiraikumar et al. [25], with some modifications. Bromoacetophenone (497.6 mg, 2.5 mmol) was taken and placed into a round-bottom flask, and then ethanol (1.25 mL) was added. The resulting reaction mixture was stirred at room temperature for 5-10 minutes until 4-bromoacetophenone was completely dissolved. After stirring for 5 minutes, benzaldehyde (265.3 mg, 2.5 mmol) was added, followed by adding 10% NaOH (1.5 mL) dropwise to the solution. The stirring of the reaction mixture was continued for 3 h with a magnetic stirrer at room temperature. The mixture was quenched with ice water and placed in an ice bath. The precipitate formed was filtered using a Buchner funnel and washed with cold water until the pH was neutral. The precipitate was dried in a desiccator and purified by recrystallization from ethanol to afford the desired product.

Synthesis of 4'-bromochalcone using microwave irradiation method (Method B)

The condition of irradiation, including reaction time and the power of irradiation in this procedure, was obtained from our orientation. The detailed process as follows: 4-bromoacetophenone (497.6 mg, 2.5 mmol) was placed into a round-bottom flask and then added with ethanol (1.25 mL). The mixture was stirred for 5 minutes at room temperature until 4-bromoacetophenone wholly dissolved. After stirring for 5 minutes, benzaldehyde (265.3 mg, 2.5 mmol) was added, followed by adding 10% NaOH (1.5 mL) dropwise to the solution. The mixture was placed in the microwave and then irradiated for 45 seconds at a power of 140 watts. The mixture was quenched with ice water and placed in an ice bath. The precipitate formed was filtered off by vacuum filtration and washed with cold water until the pH was neutral. The precipitate was dried in a desiccator and purified by recrystallization from ethanol to afford the desired product.

Physical properties evaluation of 4'-bromochalcone

The physical properties evaluation was carried out to identify the product based on observing the five senses. The synthesized product's physical properties were compared with the starting material, including appearance, colour, and odour.

Characterization of 4'-bromochalcone

Melting Point Apparatus was used to measure the melting point of the synthesized. R*f* values were determined using TLC plate with *n*-hexane: ethyl acetate = 5:1 as eluent, then visualized under UV light 254 nm. The retention time of the synthesized product was determined using GC-MS (Shimadzu QP-2010 SE) with the following condition: injector temperature = 280°C, column = Rtx-5MS, column length = 30.0 cm, pressure = 85.6 kPa, carrier gas = helium, the flow rate of carrier gas = 1.15 mL/min. FTIR, MS, and NMR ^{1}H-NMR and ^{13}C-NMR characterized the synthesized product.

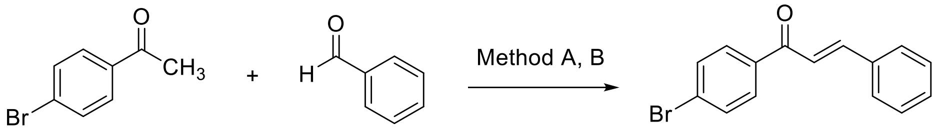
RESULTS AND DISCUSSION

Synthesis of 4'-bromochalcone using conventional and microwave irradiation methods

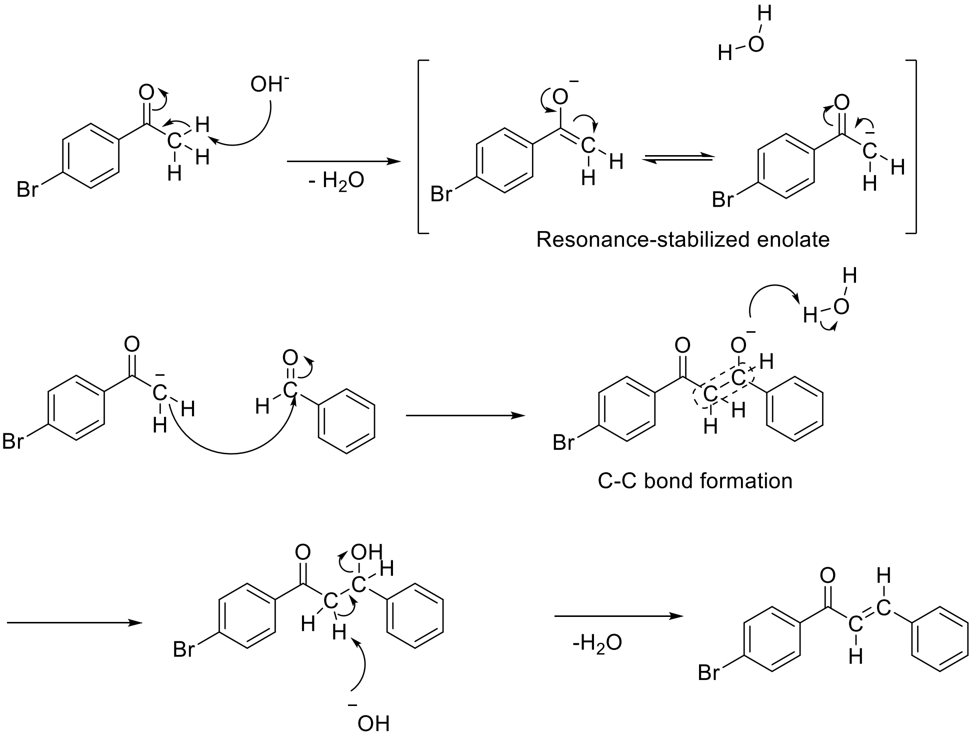
4-Bromoacetophenone was treated with benzaldehyde in the presence of a base, in which 4-bromoacetophenone was a nucleophile, whereas benzaldehyde was an electrophile. Scheme 1 illustrates the synthesis of 4'-bromochalcone was carried out by conventional methods (stirring at room temperature) and microwave irradiation. The mechanism of 4-bromochalcone formation is outlined in Scheme 2.

This reaction is commonly known as the Claisen-Schmidt reaction. This work used a 10% NaOH solution as a base catalyst. The formation of ion enolate initiates the mechanism of Claisen-Schmidt. First, Hydroxyl ions from dissociating NaOH will attack the nucleophile (4-bromoacetophenone), yielding an enolate ion. Next, the formation of a new C-C bond by nucleophilic attack of the enolate ion to the carbonyl carbon of the electrophile (benzaldehyde) [26]. The last step is the dehydration process to form 4'-bromochalcone. The selection of conventional and microwave irradiation methods was aimed to see the efficiency of these two methods. Generally, both conventional and microwave irradiation methods give a good yield, as shown in Table 1.

When applying method A (conventional method) and method B (irradiation method) to a mixture of 4-bromoacetophenone, and benzaldehyde in the presence of NaOH, it gave a pure product in 94.61±0.55% and 89.39±0.84% yield, respectively. On the other hand, Marcovicz and team reported a series of bromo- and nitro-derivatives in a good result (75-97%) when employing the Claisen-Schmidt condensation reaction with NaOH as a catalyst [24]. Furthermore, they have reported that treating 4-bromoacetophenone and benzaldehyde in alkaline condition at room temperature for 2 h, gave the 4'-bromochalchone in 76% yield. Therefore, in this work, we obtain that the synthesis of 4'bromoacetophenone using microwave irradiation gave a slightly better yield than those that Marcovicz and the team reported.



Scheme 1. The synthetic scheme of 4'-bromochalchone. Reagents and conditions: NaOH 10%, rt, 3 h (method A, conventional), NaOH 10%, irradiation 45 seconds, 140 watt (method B, irradiation)



Scheme 2. Mechanism of 4'-bromochalcone formation

Table 1. Yield and total reaction time for the synthesis of 4'-bromochalcone

Method	Replication	Isolated Amount (mg)	Theoretical Amount (mg)	Yield (%)	Average yield (%)	Reaction Time
A. Conventional	1	680.7	717.87	94.81	94.61±0.55	3 h
	2	682.4		95.05		3 h
	3	674.8		93.99		3 h
B. Irradiation	1	637.6	717.87	88.81	89.39±0.84	45 sec
	2	648.8		90.37		45 sec
	3	639.0		89.01		45 sec

Physical properties evaluation of 4'-bromochalcone

Further, we evaluated the product's physical properties, such as appearance, colour, and odour, compared to those of the starting material. And the summary of the physical properties of the product is revealed in Table 2. The product's appearance, colour, and odour were crystal powder, light yellow, and pungent odour. When compared to the starting material, it showed that the product had different appearance and colour properties from the starting material. The colour of starting material (4-bromoacetophenone) and the product showed white and light yellow, respectively.

The product's colour obtained from conventional and microwave irradiation was similar to those reported by Martelli et al. [27]. We also determine the melting range of the product using Melting Point Apparatus. The melting points of the synthesized product are presented in Table 3. According to literature reported by Lyle et al. [28], the melting point 4'-bromochalcone is 104-105 °C. Our result showed that the synthesized product's melting and melting point ranges were 103-107 °C and 1.5-4.8 °C, respectively. Due to the broadening of the melting point of the synthesized compound, we guess that our desired compound might contain impurities. We observed some small peaks of trace impurities in the ^{1}H-NMR spectra. However, in this work, we could still get one fraction of our desired compound, which has a melting point range below 2°C. This work's appearance and melting point are similar to those reported in the reference [24, 29].

Characterization of 4'-bromochalcone (TLC profile, melting point and melting range, retention time analysis)

TLC was performed to characterize and determine the R_f value of the synthesized product and the starting material. The TLC of the synthesized product is depicted in Figure 1. The TLC was accomplished using silica gel F_{254}, followed by the visualization under UV light 254 nm. The spot of the synthesized compound was compared to the starting material. The R_f values of the synthesized compound were slightly higher than those of 4-bromoacetophenone and benzaldehyde in the normal phases system. The R_f values of the synthesized compound, 4-bromoacetophenone, and benzaldehyde were 0.58, 0.51, and 0.55, respectively, when developing in *n*-hexane: ethyl acetate = 5: 1 as eluent. Shrestha et al. reported that the R_f value of 4'-bromochalcone was 0.25; when developing in *n*-hexane: ethyl acetate = 14:1 [30]. Since our eluent polarity is slightly higher than previously reported literature [30], resulting in a higher R_f value. However, the synthesized product obtained from both methods had a different Rf value than the starting material. We successfully synthesized the desired compound through conventional and microwave irradiation methods.

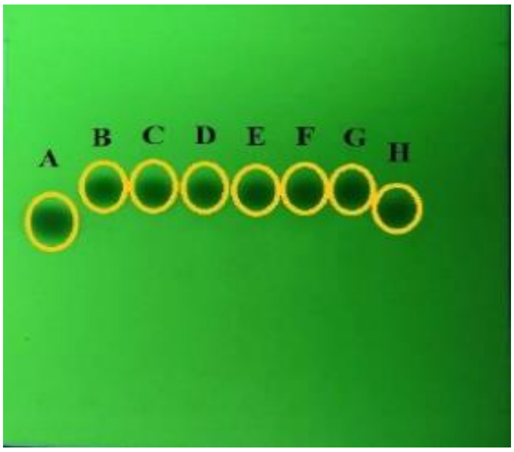


Figure 1. The TLC result of 4'-bromochalcone compared to the starting material, *n*-hexane: ethyl acetate as a mobile phase, A: 4-bromoacetophenone, B-G = 4'-bromochalcone from both two methods (conventional and irradiation microwave), H = benzaldehyde, visualized under UV light 254 nm

Table 2. Summarized the physical properties of 4'-bromochalcone

Parameters	Product obtained from each method	4-bromoacetophenone	Benzaldehyde
Appearance	Crystal powder	Crystal powder	Liquid
Color	Light yellow	White	Colorless
Odor	Strong odor	Strong odor	Strong odor

Table 3. The melting point of 4’-bromochalcone

Method	Replication	Melting point (°C)	Melting point range (°C)	References (°C) [28]
A. Conventional	1	104.5-106.3	1.8	104-105
	2	103.0-107.8	4.8	
	3	104.8-106.3	1.5	
B. Irradiation	1	104.8-107.0	2.2	
	2	104.7-107.3	2.6	
	3	103.0-106.0	3.0	

The comparison between conventional and irradiation methods, as described above, includes the yield and reaction time percentage. Moreover, the melting point, melting range, and physical properties have been compared to the reported literature. Taken together, we synthesized the desired compound by these two methods.

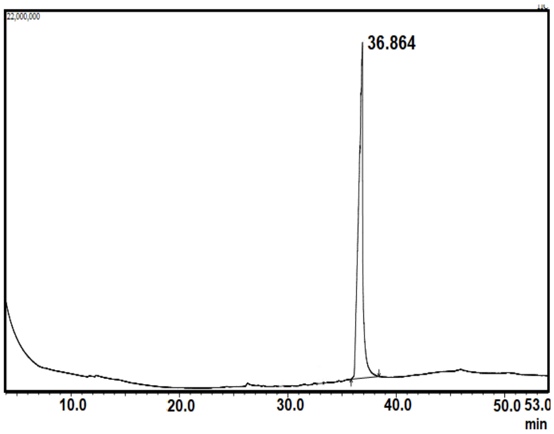


Figure 2. GC chromatogram of 4’-bromochalcone

However, we performed FTIR measurements, ^{1}H- and ^{13}C-nuclear magnetic resonance, and mass spectroscopy analyses to probe the product's structure. For this purpose, we selected the product obtained with a melting range below 2 °C, considering that the product obtained might be pure. Thus, we could get adequate spectral data.

Characterization of 4’-bromochalcone (infrared, ^{1}H- and ^{13}C-nuclear magnetic resonance, and mass spectroscopy analysis)

Another characterization was carried out using gas chromatography. It was accomplished to determine the synthesized product's retention time, and the chromatogram showed only one major peak with a retention time of 36.864 min. The chromatogram is shown in Figure 2.

FTIR measurements were conducted to identify the functional groups of all compounds. The success of the chalcone synthesis can be seen in the presence of the C=C bond absorption band in the FTIR spectrum [31]. Based on our FTIR measurement, the FTIR spectrum of the benzaldehyde as starting material showed a specific band at 1705.07 cm^{-1} that corresponds to C=O (carbonyl of aldehyde). In addition, the FTIR spectrum of 4-bromoacetophenone revealed a particular band at 1674.21 cm^{-1} that fits C=O (carbonyl of ketone). In particular, the FTIR spectrum of the synthesized product showed the absorption bands at 3024.38, 1658.78, 1604.77, 1489.05, and 825 cm^{-1}, as depicted in Figure 3.

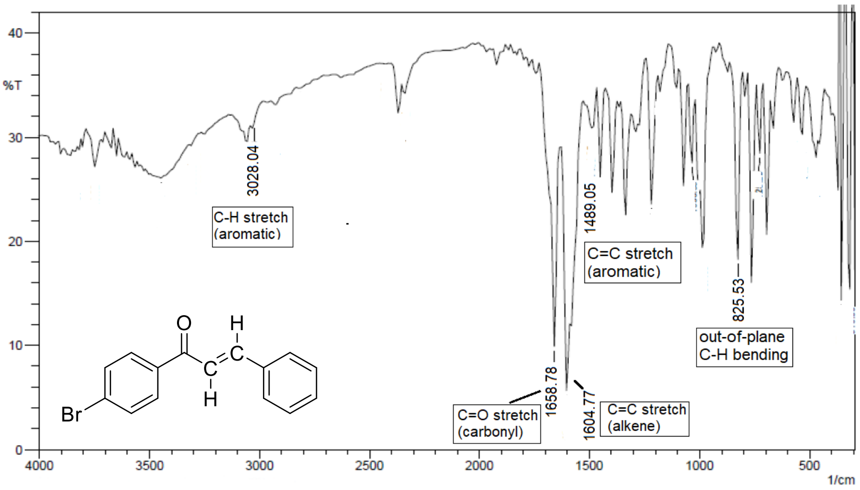
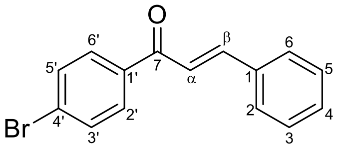


Figure 3. The FTIR spectrum of 4'-bromochalcone

Table 4. Summarized ^{1}H-NMR and ^{13}C-NMR spectral data of 4'-bromochalcone

Structure	Spectral data
	**^{1}H-NMR** (500 MHz, acetone-*d6*) 8.10-8.08 (m, 2H), 7.87-7.82 (m, 4H), 7.78-7.75 (m, 2H), 7.48-7.46 (m, 3H). **^{13}C-NMR** (125 MHz, acetone-*d6*) 189.1, 145.4, 138.1, 135.9, 132.7, 131.5, 131.2, 129.8, 129.6, 128.1, 122.5

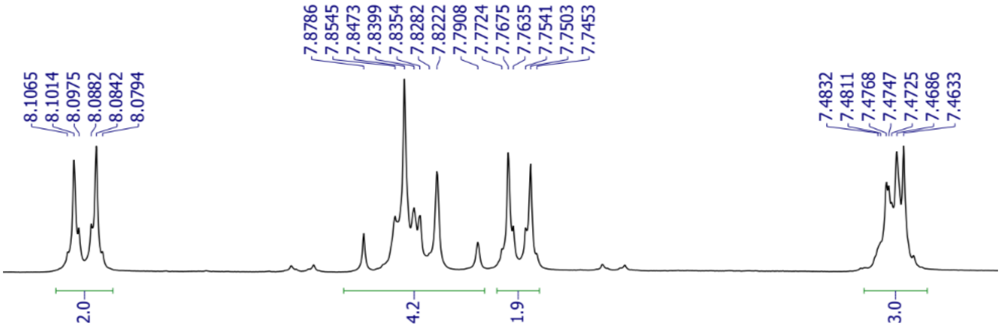


Figure 4. ^{1}H-NMR spectrum of 4'-bromochalcone

The bands at 3024.38 and 1489.05 cm^{-1} correspond to the C-H stretch (aromatic) and C=C stretch (aromatic), respectively. The band at 1658.78 cm^{-1} was assigned for C=O (carbonyl) stretch vibration. The band at 1604.77 cm^{-1} corresponds to the C=C stretch with strong intensity. The C=C band of 4'-bromochalcone (1604.77 cm^{-1}) is in line with the literature that the C=C band of chalcone analogue compounds appears at 1601 cm^{-1} [32]. In addition, the band at 825 cm^{-1} could be attributed to out-of-plane C-H bending for the para-substituted benzene ring. All these infrared data suggest the successful formation of the desired chalcone.

The signals of Hα and Hβ in the ^{1}H-NMR should be precise (Figure 4). It will appear as two doublet signals with a coupling constant

(*J* values) of 15-16 Hz. However, in this result, the signals of Hα and Hβ overlap with other peaks, so we could not identify them clearly, especially for Hα and Hβ including their *J* values. It might be caused by the effect of the deuterium solvent used in the ^{1}H-NMR measurement.

In the reported literature by [24, 33], the chemical shift of Hα and Hβ using $CDCl_3$ solvent appears as a doublet signal around 7.47 and 7.82 ppm (*J* = 15.7 Hz), respectively. Here, we could notice that the type of deuterated solvent used in the ^{1}H-NMR measurement could affect the chemical shift of protons [33]. However, we could still characterize our synthesized product using ^{13}C-NMR and mass spectrometry. Further, we analyzed the synthesized product using ^{13}C-NMR to identify the number of carbon. The spectrum of ^{13}C-NMR is presented in Figure 5. The peak at 189.1 ppm is due to the carbon-oxygen double bond (C=O). The peaks at 145.4 and 128.1 ppm are due to the C=C bond (Cα and Cβ). Other peaks belong to aromatic carbon. The ^{13}C-NMR spectrum obtained in this result follows the reported literature [24]. In addition, we performed mass spectrometry analysis to confirm the molecular weight of the synthesized product. According to the mass spectrum analysis, the molecular ion peak, $[M+H]^+$, was found at m/z 287. The mass spectrum of the synthesized product is exhibited in Figure 6. Overall, the characterization of the synthesized product revealed that the obtained product was the expected compound.

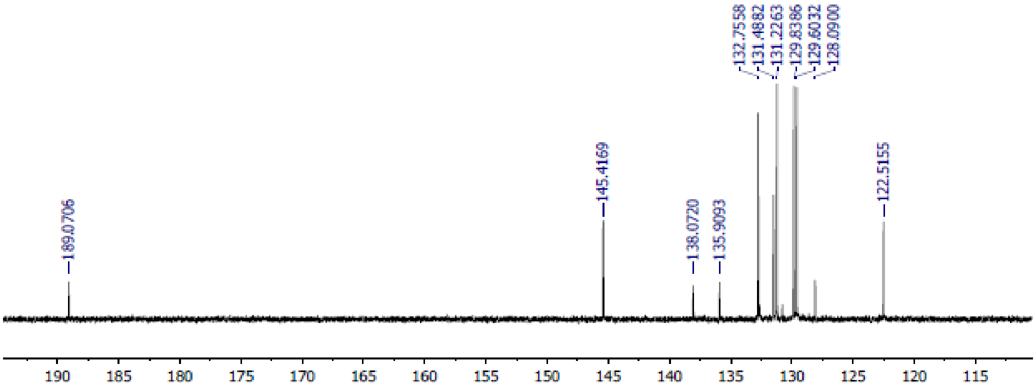


Figure 5. ^{13}C-NMR spectrum of 4’-bromochalcone

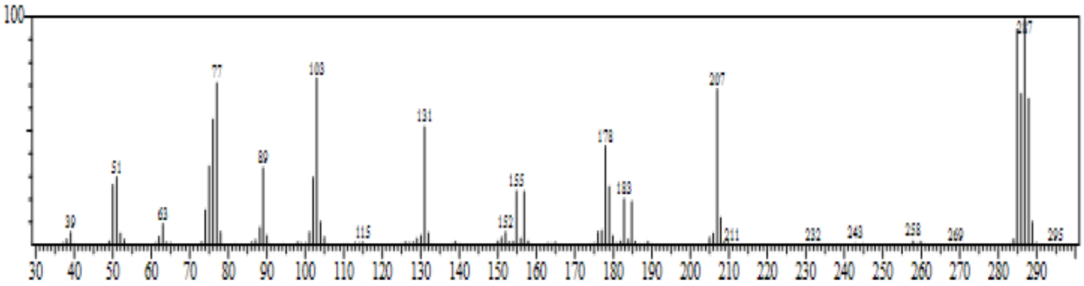


Figure 6. Mass spectrum of 4’-bromochalcone

CONCLUSION

4’-Bromochalcone has been successfully synthesized using conventional and microwave irradiation methods in 94.61%±0.6793 and 89.39%±0.6418 yield, respectively. The compound's physicochemical properties evaluation and spectral data analysis showed that the synthesized product was 4’-bromochalcone. Synthesis of 4’-bromochalchone using microwave irradiation could be done in a shorter time than the conventional method with a total reaction of 45 s and 3 h, respectively.

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