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Research Article

Microwave-Assisted Method for Synthesizing UV-Protective Methoxy-Benzylidene Cyclohexanone Derivatives Using Green Solvents

Muchammad Ikmal Abdillah[1], Dayu Arinda[1], Dini Rohmawati[1], Cornelia Budimarwanti[1], Sri Handayani[1*]

[1]Department of Chemistry Education, Faculty of Mathematics and Natural Sciences, Universitas Negeri Yogyakarta, Karangmalang, Yogyakarta, 55281, Indonesia

[*]Email: handayani@uny.ac.id

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Abstract

Benzylidene cyclohexanone derivatives are known for their significant biological activities; however, traditional synthesis methods often involve non-eco-friendly processes and solvents. This research aims to identify the optimal solvent for maximum yield and to evaluate the UV-protection activity. The synthesis was conducted through a Claisen-Schmidt condensation reaction under NaOH catalysis with microwave irradiation for 60 seconds. Solvents tested included H_2O, H_2O/MeOH (1:1 v/v), H_2O/EtOH (1:1 v/v), MeOH, and EtOH. Reaction purity was assessed using TLC scanning. The product with the highest purity was recrystallized from EtOH and characterized by melting point, UV-Vis, FT-IR, ^{1}H-NMR, and GC-MS analysis. The UV-protection activity was evaluated *in vitro*. The results indicate the successful synthesis of two benzylidene cyclohexanone derivatives: (2E,6E)-bis(4-methoxybenzylidene) cyclohexanone (yellow needles) and (E)-2-(4-methoxybenzylidene) cyclohexanone (orange). The H_2O/MeOH (1:1 v/v) solvent provided the highest yields of 58.49% and 62.71%, respectively. The (2E,6E)-bis(4-methoxybenzylidene) cyclohexanone demonstrated a high SPF value of 9.908, offering maximum protection at 50 ppm concentration, while the mixed compound, (E)-2-(4-methoxybenzylidene) cyclohexanone, achieved an SPF of 15.324, categorized as ultra protection.

Keywords: Benzylidene cyclohexanone, green synthesis, microwave-assisted, solvent, sun protection factor

1. INTRODUCTION

The development of the pharmaceutical industry is based on the process of discovering drugs from the synthesis of compounds that have extensive potential biological and pharmacological activity. Various studies prove the wide range of pharmaceutical and medical applications of α,β-unsaturated ketones, such as antibacterial[1], antioxidant[2], antiproliferative[3], and anticancer[4,5] activities. Benzylidene cyclohexanone is classified as an α,β-unsaturated ketone, which is reported to have higher stability, pharmacokinetic profile, anti-inflammatory, and antioxidant activity compared to curcumin[6]. In addition, the cyclohexanone structure as the center can inhibit the growth of ovarian, colon, and breast cancer cells better than cisplatin[7]. The derivative structure of benzylidene cyclohexanone contains a conjugated double bond and an aromatic ring, which allows for resonance and UV light absorption[8]. The efficacy of benzylidene cyclohexanone derivatives as sunscreens and their UV protection ability can be determined by calculating the Sun Protection Factor (SPF) value with *in vitro* screening methods. The synthesis of sunscreen agent compounds also contributes to the achievement of Sustainable Development Goal (SDG) 3, which is good health and well-being[9]. Benzylidene cyclohexanone is generally synthesized through the Claisen-Schmidt condensation reaction.

The sustainability and environmental impact of the Claisen-Schmidt condensation reaction continue to be developed by many researchers, including the use of variations in solvent. Some of the solvents that have been used in the synthesis of α,β-unsaturated ketones

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via Claisen-Schmidt condensation are organic solvents such as ethanol[10], methanol[11], dichloromethane[12]; ionic liquid[13]; water[14]; and mixed solvent such as water/cyclohexane (1:1), water/toluene (1:1), water/ethanol (1:1)[15]. In the manufacture of Active Pharmaceutical Ingredients (API), organic solvents play a major role, contributing 56% of the total weight (wt. %) in the entire process, and contribute to 80% of the total organic waste[16]. Not only causing environmental problems, but the use of organic solvents also has the potential to cause health problems due to their volatility and toxicity[17,18]. Therefore, the search for alternative solvents that are more environmentally friendly (green solvents) is important to overcome these problems. Additionally, the use of green solvents also supports the implementation of SDG 12, which is responsible consumption and production[19].

The role of solvents in organic synthesis not only facilitates the formation of homogeneous solutions but also affects the reaction rate, selectivity, and yield[20]. In addition to choosing a solvent that provides the greatest reaction effectiveness, solvent selection also needs to consider several properties that embody the characteristics of green solvents, such as low toxicity, safe to use (non-flammable, non-explosive), abundant in nature, cheap, easy to obtain, and easy to separate[21]. The most common strategies for choosing a solvent that produces the lowest environmental impact are the Environment, Health, and Safety (EHS) and Life Cycle Assessment (LCA) methods. Based on both methods, methanol and ethanol provide the best score compared to 24 other organic solvents[22]. In addition, adding water as a cosolvent can reduce the harmful effects (lower the EHS score) of methanol and ethanol solvents since water has an EHS score equal to zero, in other words, it is categorized as the safest solvent to use and is not toxic[23,24].

The use of the microwave-assisted method is considered a green approach in organic synthesis due to the ability to increase reaction rate and product yield compared to the conventional method[25,26]. Moreover, it also supports SDG 7, which aims to enhance energy efficiency, and SDG 12 by reducing by-products and chemical waste in a reaction[27]. Current synthetic methods for benzylidene cyclohexanone derivatives are often hindered by prolonged reaction times and a heavy reliance on hazardous organic solvents, resulting in high energy consumption and significant environmental and health risks. To address these challenges, this study evaluates the synthesis of these compounds using a microwave-assisted method and a variety of green solvent systems as a more sustainable alternative. This approach aims to enhance energy efficiency and minimize toxic waste while maintaining high yields and selectivity for both mono- and bis-substituted derivatives and evaluate one of their broad biological and pharmacological activities, specifically their UV protection.

2. RESEARCH METHODS

Materials

The materials, including cyclohexanone, 4-methoxybenzaldehyde, sodium hydroxide, distilled water, methanol, ethanol, chloroform, and *n*-hexane, were purchased from Merck (Germany) in pro analysis specification.

Instrumentation

The microwave that was used for synthesis was an Electrolux microwave oven EMM2007X. Spot identification was performed with the CAMAG® UV Cabinet 4, and the purity determination was performed with the CAMAG® TLC Scanner 4 Densitometer. The melting points were determined using the melting point apparatus MPTD-1 220 V/50 Hz. Structure elucidation was carried out using a UV-Vis spectrophotometer SHIMADZU UV-2450, an FT-IR type IRPrestige-21 SHIMADZU (with KBr pellet method), a ^{1}H-NMR JNM-ECZ500R 500 MHz Super Conductive Magnet ($CDCl_3$ was used as the deurated solvent for NMR measurement), and a GC-MS-QP2010S SHIMADZU.

Synthesis of (2E,6E)-bis(4-methoxybenzylidene) cyclohexanone Using Various Solvents (A1-A5)

Five mmol of sodium hydroxide was dissolved in 2 mL H_2O was placed in a porcelain crucible. Cyclohexanone (5 mmol) and 4-methoxybenzaldehyde (10 mmol) were added consecutively (**Figure 1**). The mixture was irradiated with microwaves for ten seconds and repeated six times, to ensure that the reaction was complete. Afterwards, the product was weighed. The procedure was repeated by replacing H_2O with other solvent variations, which were H_2O/MeOH (1:1 v/v), MeOH, H_2O/EtOH (1:1 v/v), and EtOH. To determine the purity of the product, TLC was carried out with *n*-hexane: chloroform (1:2 v/v). Furthermore, it was scanned using the TLC Scanner. Hence, the %yield was determined. The yellow solid product with the highest purity was recrystallized from EtOH. Then, it was characterized by melting point determination, UV-Vis, FT-IR, ^{1}H-NMR, and GC-MS. The **A2 compound** exhibited the following characteristics. Yield: 58.49%. Yellow needles. Recrystallized from EtOH. M.P: 160-161.9 °C. UV (EtOH): 358.50 nm. IR (KBr, cm^{-1}): 2939 (**C-H** stretch), 1658 (**C=O** stretch), 1597 (**C=C** alkene stretch), 1556, 1508 (**C=C** aromatic stretch), 1458 (**CH_2** bend), 1249 (**C-O** stretch), 835 (***p*-disubstituted benzene ring**). ^{1}H-NMR ($CDCl_3$): δ 7.76 (s, 2H, J = -), δ 7.43 (d, 4H, J =

9.0 Hz), δ 6.91 (d, 4H, J = 9.0 Hz), δ 3.81 (s, 6H, J = -), δ 2.88 (t, 4H, J = 6.6 Hz), and δ 1.77 (m, 2H, J = 6.5 Hz). MS (*m/z*): 28, 39, 51, 65, 77, 91, 103, 115,121, 128, 153, 159, 171, 184, 199, 215, 235, 247, 263, 275, 277, 291, 303, 319, 333 (base peak), 334 [M^+], and 336 [$M+2$].

Synthesis of (E)-2-(4-methoxybenzylidene) cyclohexanone Using Various Solvents (B1-B5)

Dissolved 3 mmol sodium hydroxide in 2 mL H_2O was placed in a porcelain crucible. Cyclohexanone (2 mmol) and 4-methoxybenzaldehyde (0.5 mmol) were added consecutively (**Figure 2**). Irradiated with microwaves for ten seconds and repeated six times, to ensure that the reaction is complete. Repeat the procedure by replacing H_2O with other solvent variations, which were H_2O/MeOH (1:1 v/v), MeOH, H_2O/EtOH (1:1 v/v), and EtOH. To determine the purity of the product, TLC was carried out with *n*-hexane: chloroform (1:2 v/v). Furthermore, it was scanned using the TLC Scanner. Hence, the %yield could be determined. The orange solid product with the highest purity was acidified in HCl and washed with water, then recrystallized with EtOH. Then, it was characterized by UV-Vis, FT-IR, and ^{1}H-NMR. **B2 compound**. Yield: 62.71%. Orange. Recrystallized from EtOH. UV (EtOH): 225 nm. IR (KBr, cm^{-1}): 2932 (**C-H** stretch), 1705 (**C=O** stretch), 1605 (**C=C** alkene stretch), 1512 (**C=C** aromatic stretch), 1458 (**CH_2** bend), 1249, 1034 (**C-O** stretch), 833 (***p*-disubstituted benzene ring**). ^{1}H-NMR ($CDCl_3$): δ 7.23 (s, 1H, J = -), δ 7.07 (d, 2H, J = 10 Hz), δ 6.82 (d, 2H, J = 10 Hz), δ 3.80 (s, 3H, J = -), δ 3.26 (t, 2H, J = -), δ 2.07 (t, 2H, J = -), δ 1.75 (m, 2H, J = -) and δ 1.71 (m, 2H, J = -).

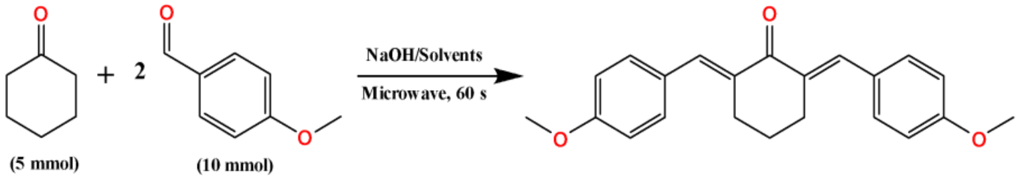


Figure 1. Synthesis of (2E,6E)-bis(4-methoxybenzylidene) cyclohexanone compound

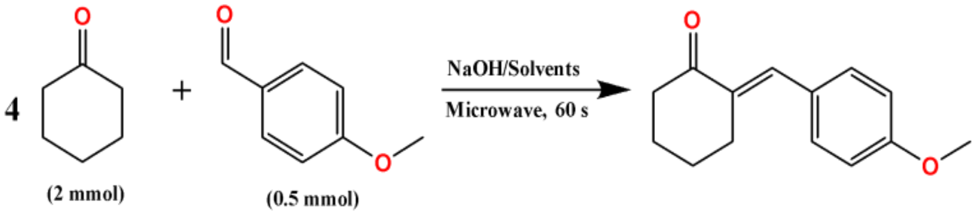


Figure 2. Synthesis of (E)-2-(4-methoxybenzylidene) cyclohexanone compound

Determination of SPF Value In Vitro

The SPF value of the synthesized compounds was determined by preparing a 100 ppm stock solution in 96% EtOH, with a total volume of 100 mL. This stock solution was then diluted to obtain concentrations of 10 ppm, 20 ppm, 30 ppm, 40 ppm, and 50 ppm. Each concentration variation was measured at wavelengths ranging from 290 to 320 nm, with 5 nm intervals, using a UV-Vis spectrophotometer. The SPF values were then calculated using the Mansur equation (1).

$$SPF_{spectrophotometric} = CF \times \sum_{290}^{320} EE(\lambda) \times I(\lambda) \times Abs(\lambda) \quad (1)$$

Where, EE(λ) = spectrum thermal effect; I(λ) = spectrum intensity; Abs(λ) = absorbance value; CF = correction factor (10). The determination of SPF is the correlation between **EE(λ)** and **I(λ)** shown in **Table 1**[28]. After the SPF value is known, it is categorized based on the protection that provides evidence of the sunscreen's ability to protect the skin as shown in **Table 2**[29].

Table 1. The correlation between EE(λ) and I(λ)

λ (nm)	EE(λ)×I(λ)
290	0.0150
295	0.0817
300	0.2874
305	0.3278
310	0.1864
315	0.0839
320	0.0180

Table 2. SPF protection ability

SPF Value	Protection Ability
2–4	Minimum
4–6	Moderate
6–8	Extra
8–15	Maximum
>15	Ultra

3. RESULT AND DISCUSSION

Identification of Benzylidene Cyclohexanone Derivatives

The base-catalyzed Claisen-Schmidt condensation mechanism proceeds via the enolate pathway, with the enolate ion serving as the primary intermediate in the aldol condensation that forms *α,β*-unsaturated ketone products. Due to the strength of NaOH as a base, the carbonyl compound is fully converted to enolate ions[30]. The mechanism of the Claisen-Schmidt condensation reaction is shown in **Figure 3**.

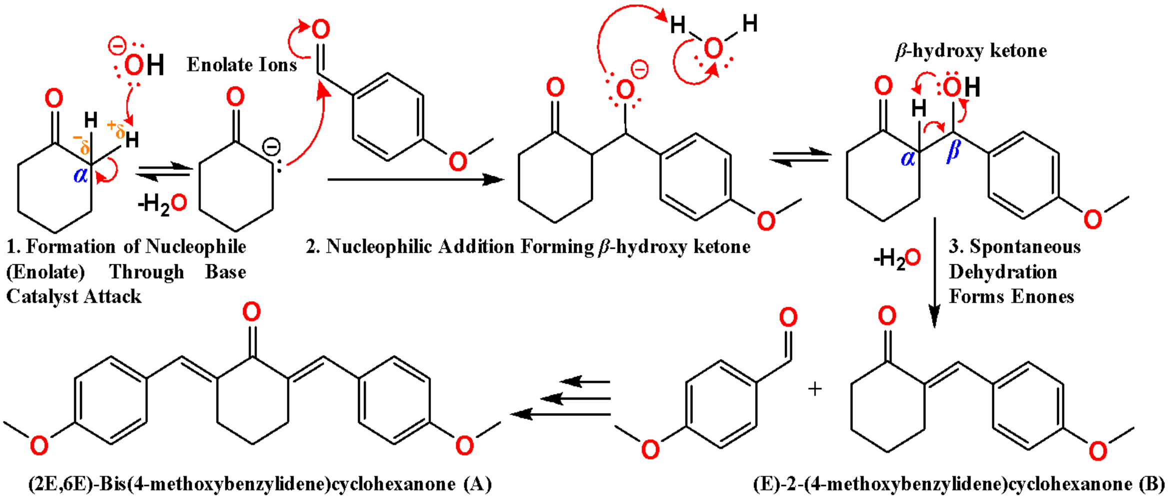


Figure 3. The mechanism of the Claisen-Schmidt condensation reaction

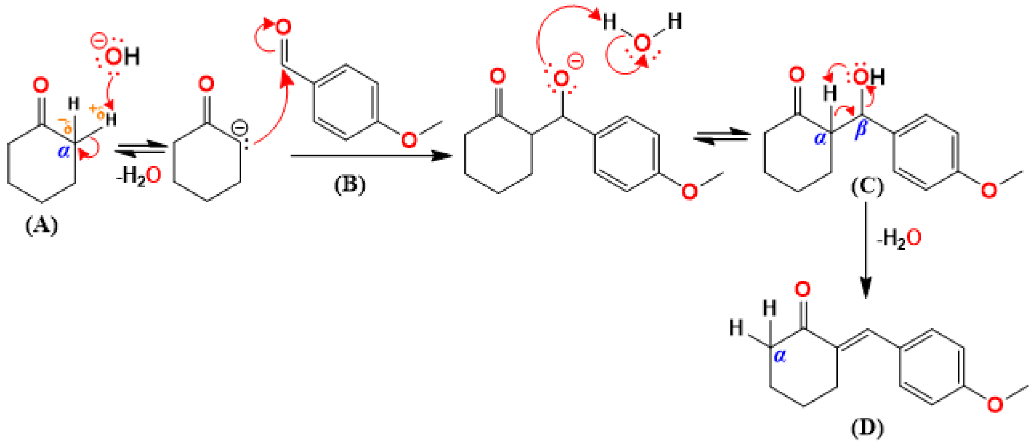


Figure 4. The mechanism for the formation of the (E)-2-(4-methoxybenzylidene) cyclohexanone compound

In general, Claisen-Schmidt condensation produces the E isomer of the enone[31]. Trans or E (*Entgegen*) isomers of *α,β*-unsaturated carbonyl compounds can exist without steric hindrance in the plane of the C=C double bond. This geometry allows for taking full advantage of the resonance stabilization; hence, this product is more stable. On the other hand, in the cis or Z (*zusammen*) isomers of *α,β*-unsaturated carbonyl compounds the presence of substituents at the ends of the C=C double bond is hindered, preventing a planar geometry and consequently resonance stabilization is reduced[32].

The molar ratio of cyclohexanone and 4-methoxybenzaldehyde for synthesizing (2E,6E)-bis(4-methoxybenzylidene) cyclohexanone **(A)** is 1:2, because cyclohexanone has *α*-hydrogen on both sides of the carbonyl carbon, which allows it to undergo further reactions. Therefore, to optimize the formation of the bis-product and avoid the possibility of forming a mono-product, an excess amount of 4-methoxybenzaldehyde moles are used compared to cyclohexanone moles. Thus, the enolate ion mono-product that has formed at the beginning can attack again and react with the second 4-methoxybenzaldehyde molecule[33]. However, the synthesis of (E)-2-(4-methoxybenzylidene) cyclohexanone **(B)** was carried out using a 4:1 molar ratio of cyclohexanone to 4-methoxybenzaldehyde. This excess of the ketone donor is consistent with previous studies showing that a molar excess of cyclohexanone promotes selective formation of the mono-condensation product; without sufficient excess, a competing reaction leads to formation of a di-substituted by product[11,34]. This occurs because the mono-benzylidene intermediate can react more rapidly with residual aldehyde than cyclohexanone itself, resulting in kinetic competition that favors double condensation. Maintaining a high cyclohexanone concentration therefore reduces the probability of this secondary reaction, kinetically limiting formation of (2E,6E)-bis(4-methoxybenzylidene) cyclohexanone[35]. The mechanism for the formation of the (E)-2-(4-methoxybenzylidene) cyclohexanone compound is shown in **Figure 4**.

The use of excess cyclohexanone **(A)** ensures that the 4-methoxybenzaldehyde **(B)** reacts preferentially with the starting cyclohexanone rather than with the newly formed mono-adduct **(D)**.

TLC and TLC scanner identification with *n*-hexane: chloroform (1:2 v/v) eluent formed a spot area on the chromatogram visible as a fluorescence region. The *n*-hexane: chloroform (1:2 v/v) eluent used was selected by trial and error. This eluent gave a good separation spot and is still in the range of good Rf values of 0.2-0.8[36]. Data on the synthesized compounds for each solvent variation are shown in **Table 3**.

Table 3. Synthesis result data of each solvent variation

Code	Solvent Ratio (2 mL)	Colour	Product Weight (g)	Rf	Purity (%)	Yield (%)
A1	H_2O	Yellow	1.055	0.520	7.77	4.90
A2*	H_2O/MeOH (1:1)	Yellow	1.490	0.552	65.63	58.49
A3	H_2O/EtOH (1:1)	Yellow	1.584	0.535	27.93	26.46
A4	MeOH	Yellow	2.327	0.570	28.34	39.44
A5	EtOH	Yellow	2.516	0.530	27.34	41.14
B1	H_2O	Orange	2.389	0.341	4.43	9.80
B2*	H_2O/MeOH (1:1)	Orange	2.815	0.336	24.06	62.71
B3	H_2O/EtOH (1:1)	Orange	2.996	0.345	18.59	51.57
B4	MeOH	Orange	3.282	0.332	15.58	47.35
B5	EtOH	Orange	3.307	0.375	19.57	59.92

*⁾ target compounds with the highest purity are identified and further characterized

Compounds A2 and B2 exhibited the highest purity and were thus purified via recrystallization using EtOH. Crystal A2 displayed a melting point of 160–161.9 °C, indicating its high purity, as evidenced by the narrow melting point range (<2 °C)[33] melting point aligns with the reference value for (2E,6E)-bis(4-methoxybenzylidene) cyclohexanone, which is reported as 160–162 °C[37]. On the contrary, B2 crystals displayed impurity and were suspected to contain a mixture of compounds, thus melting point determination was omitted to avoid inaccurate data.

Characterization of A2 and B2 Compound

Characterization by UV-Vis spectrophotometer was carried out with starting material 4-methoxybenzaldehyde (X), compounds A2, and B2 were measured at λ 200-800 nm, 0.5 nm interval, with 96% EtOH solvent. The absorbance spectra data obtained were compared to obtain information on the formation of a new conjugated double bond (C=C), which can predict the formation of a chromophore group. The longer the chromophore with conjugated double bonds, the lower the energy for the $\pi \rightarrow \pi^*$ transition, as a result λ_{max} will shift towards the longer because absorption in the UV region depends on the electronic structure of a compound, the freer the delocalization of electrons, the easier it will be for electrons to undergo electronic transitions, the energy will be smaller, consequently λ will be greater[38,39]. Based on the measurement results between the starting material and the target compound, there is a λ shift towards a longer (bathochromic shift), which is shown by the results of the absorbance spectrum of the λ_{max} measurement of the starting material 4-methoxybenzaldehyde (X), compounds A2, and B2 in **Figure 5** of 270.0 nm, 358.50 nm, and 285.00, respectively. The estimated transition electron and chromophore data of starting material 4-methoxybenzaldehyde (**X**), compounds **A2**, and **B2** are shown in **Table 4.**

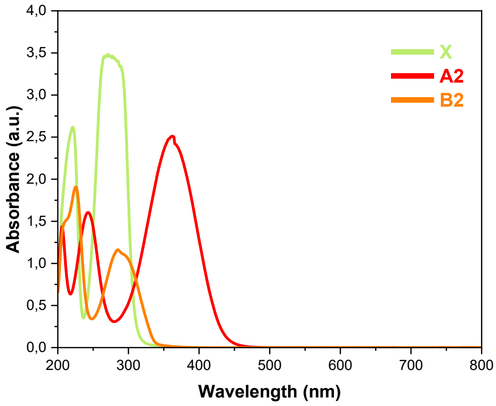


Figure 5. Absorbance spectra of 4-methoxybenzaldehyde (X), compounds A2 and B2

Table 4. Predicted electron & chromophore transitions

Compound	λ_{max} (nm)	Electron Transition	Chromophore	Absorbance (A)
X	270.50	$n \rightarrow \pi^*$	C=O	3.482
	221.00	$\pi \rightarrow \pi^*$	C=C	2.618
A2	358.50	$n \rightarrow \pi^*$	C=O	2.256
	243.00	$\pi \rightarrow \pi^*$	C=C	1.635
	206.50	$n \rightarrow \sigma^*$	C–O	1.538
B2	285.00	$n \rightarrow \pi^*$	C=O	1.162
	225.00	$\pi \rightarrow \pi^*$	C=C	1.907

These results show that compounds A2 and B2 have a longer λ_{max} than the starting material 4-methoxybenzaldehyde (X) due to the formation of π bonds or the addition of new conjugated double bonds (C=C), which support the formation of compounds that are different from the starting material 4-methoxybenzaldehyde (X).

The IR spectra in **Figure 6** show that compounds A2 and B2 contain C-H aliphatic sp^3 (stretching), C=O carbonyl (stretching), C=C alkene (stretching), CH_2 methylene (bending), C=C aromatic (stretching), C-O (stretching), and aromatic substituted in the para position.

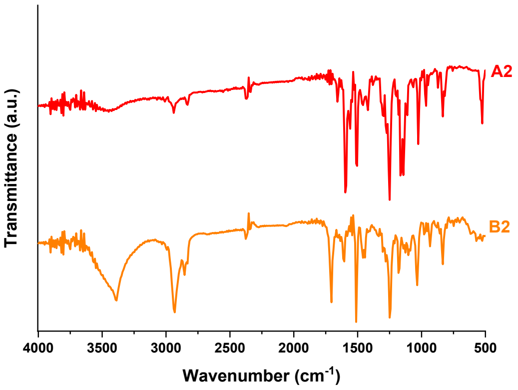


Figure 6. IR spectra A2 and B2 compound

The key difference in the IR spectrum between compounds A2 and B2 lies in the absorption region of the C=O carbonyl stretching, conjugated with a double bond. For compound A2, this absorption appears at 1658 cm^{-1}, while for compound B2, it is observed at 1705 cm^{-1}. Typically, the C=O absorption in ketones falls around 1725-1705 cm^{-1}, and for aldehydes, it is generally in the 1740-1720 cm^{-1}[39]. The lower C=O absorption frequency in A2, compared to B2, is due to electronic effects from structural differences: A2 likely contains two conjugated double bonds flanking the C=O group, while B2 likely has only one conjugated double bond. The presence of an electron-donating group (-OCH_3) enhances electron delocalization toward the carbonyl, reducing the double bond character and thereby lowering the C=O vibrational frequency. Resonance effects can also lower the C=O stretching frequency, as the single bond between the carbon and oxygen atoms transforms into a double bond in equilibrium, thus weakening the C=O bond strength[38]. The delocalization of π-electrons in conjugated systems typically results in a lower absorption frequency for the C=O group[8]. Generally, α,β-unsaturated carbonyl bond experience a frequency reduction of 25-45 cm^{-1} from the baseline value[39].

To support the FT-IR data, the target compounds were analyzed using ^{1}H-NMR. ^{1}H-NMR characterization results of compounds A2 and B2 are shown in **Figures 7** and **8**.

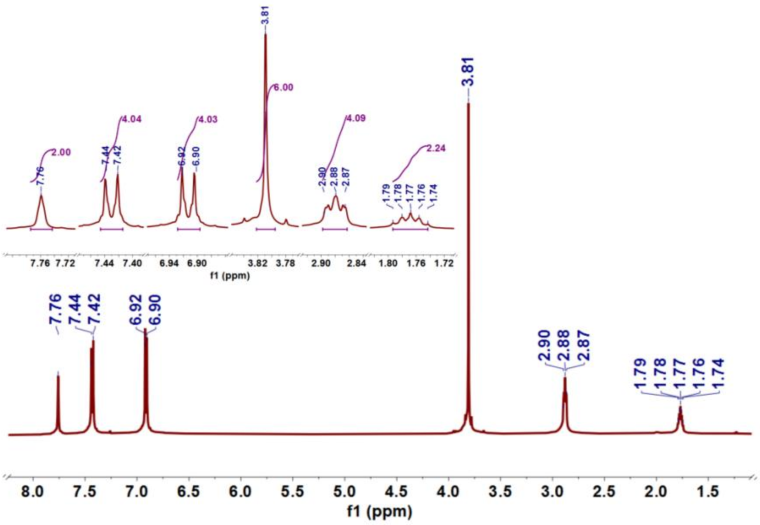


Figure 7. ^{1}H-NMR characterization results of A2 compound

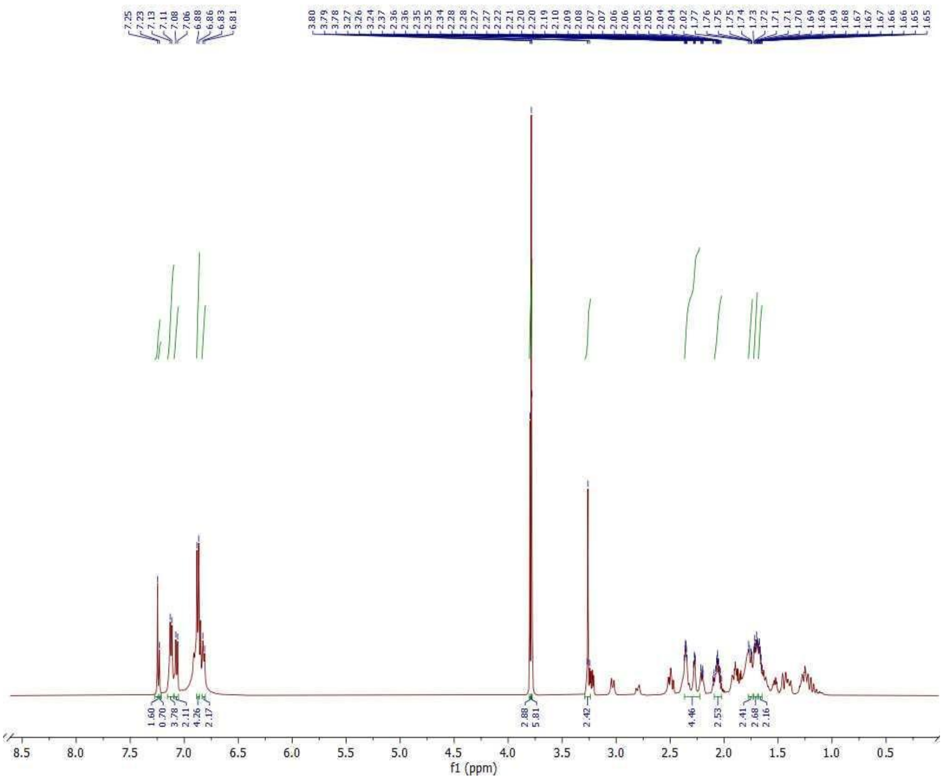
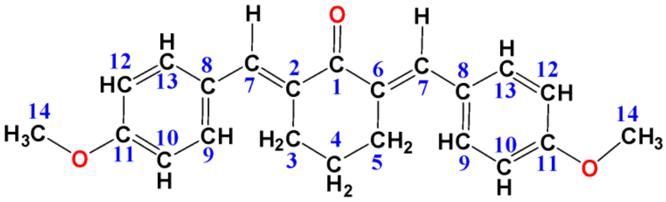


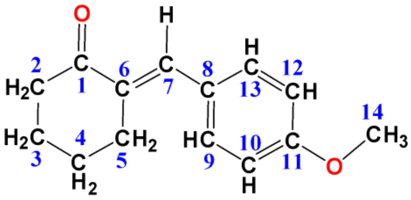
Figure 8. ^{1}H-NMR characterization results of B2 compound

Table 5. Analysis result data δ ($\sum$H, m, J Hz) ppm

A2



B2



No C	Ref (Kar *et al.*,[37]) (CDCl$_3$, 400 MHz) δ ($\sum$H, m, J Hz) ppm	Compound A2 (CDCl$_3$, 500 MHz) δ ($\sum$H, m, J Hz) ppm	No C	Ref (Puteri & Handayani,[35]) (CDCl$_3$, 400 MHz) δ ($\sum$H, m, J Hz) ppm	Compound B2 (CDCl$_3$, 500 MHz) δ ($\sum$H, m, J Hz) ppm
1	-	-	**1**	-	-
2, 6	-	-	**2**	2,92 (2H, t, -)	3.26 (2H, t, -)
3, 5	2.92 (4H, t, 6.5)	2.88 (4H, t, 6.6)	**3**	1.84 (2H, m, -)	1.71 (2H, m, -)
4	1.81 (2H, m, 6.5)	1.77 (2H, m, 6.5)	**4**	2,36 (2H, m, -)	1.75 (2H, m, -)
7	7.76 (2H, s, -)	7.76 (2H, s, -)	**5**	2.82 (2H, t, -)	2.07 (2H, t, -)
8	-	-	**6**	-	-
9, 13	7.45 (4H, d, 7.6)	7.43 (4H, d, 9.0)	**7**	7.76 (1H, s, -)	7.23 (1H, s, -)
10, 12	6.93 (4H, d, 7.6)	6.91 (4H, d, 9.0)	**8**	-	-
11	-	-	**9, 13**	7.11 (2H, d, -)	7.07 (2H, d, 10)
14	3.84 (6H, s, -)	3.81 (6H, s, -)	**10, 12**	6.86 (2H, d, -)	6.82 (2H, d, 10)
			11	-	-
			14	3.85 (3H, s, -)	3.80 (3H, s, -)

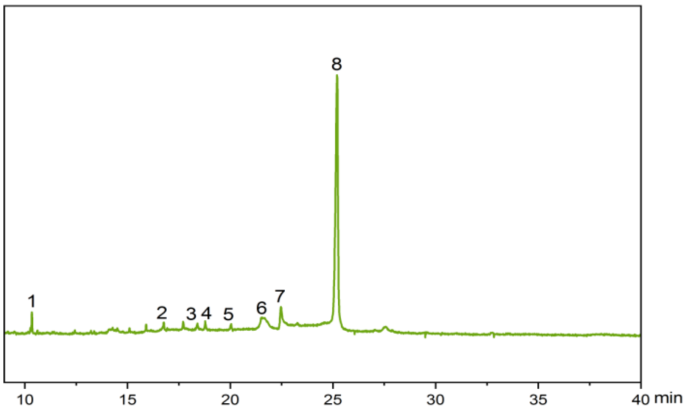
Based on the results of ^{1}H-NMR characterization, the spectra were analyzed to determine the type, number, and environment of hydrogen atoms (protons) as shown in **Table 5**.

The ^{1}H-NMR spectrum of compound **A2** reveals six types of protons. A multiplet at 1.77 ppm and a triplet at 2.88 ppm correspond to methylene protons. A singlet at 7.76 ppm indicates the presence of alkene protons. Methoxy protons appear at 3.81 ppm, while aromatic protons are observed as doublets at 6.91 ppm (shielded) and 7.43 ppm (deshielded), with J-coupling constants of 9.0 Hz, indicating ortho coupling. These values align with the expected chemical shifts for aromatic protons at δ 6.5–8.0 ppm, and *J*-coupling constants for ortho aromatic protons, typically between 7.0 and 10.0 Hz[39]. The six observed peaks closely matched the chemical shifts reported in previous research[37,40] supporting the structural assignment of compound **A2** as (2E,6E)-bis(4-methoxybenzylidene)cyclohexanone[40].

In compound B2, 14 distinct proton signals were identified. The types of protons identified exceed the types of protons that should appear. Thus, it can be assumed that the synthesized compound is still a mixed compound. Other peaks that appear are assumed to be peaks of the compound (2E,6E)-bis(4-methoxybenzylidene) cyclohexanone due to further reactions. There were also small overlapping multiplet peaks in the region of 1-1.5 ppm; these peaks were assumed to be compounds resulting from self-aldol condensation reactions between cyclohexanones. However, 8 types of protons appeared indicating the presence of the target compound, namely (E)-2-(4-methoxybenzylidene) cyclohexanone including two multiplet peaks at 1.71 ppm and 1.75 ppm, two triplet peaks at 2.07 ppm and 3.26 ppm of a methylene group. Singlet peak at 7.23 ppm indicates the presence of alkene protons. Methoxy protons were indicated by a singlet peak at 3.80 ppm. Aromatic protons appeared as two doublet peaks at 6.82 ppm (shielding) and 7.07 ppm (deshielding) supported by constant *J*-coupling values of 10.0 Hz and 10.0 Hz (ortho coupling), respectively.

To confirm the molecular weight, compound A2 was analyzed using GC-MS which showed a high purity chromatogram peak of 75.80% as shown in **Figure 9**. The mass spectrometer **Figure 10** also displayed a molecular ion of m/z 334.

Compound (2E,6E)-bis(4-methoxybenzylidene) cyclohexanone has a molecular weight of 334.4 g/mol[41]. Thus, these data confirm that compound A2 has the structural correctness as compound (2E,6E)-bis(4-methoxybenzylidene) cyclohexanone.



Peak#	R.Time	I.Time	F.Time	Area	%Area	Height
1	10.293	10.217	10.542	380984	2.43	25090
2	16.769	16.617	16.892	201390	1.28	42041
3	18.411	18.217	18.517	189041	1.20	31480
4	18.792	18.517	18.967	199690	1.27	40718
5	20.042	19.892	20.142	168322	1.07	32301
6	21.524	21.242	22.192	1553206	9.89	60743
7	22.477	22.342	22.917	1106824	7.05	109550
8	25.208	24.817	25.517	11902524	75.80	1358667
	Σ			15701981	100.00	1700590

Figure 9. GC chromatogram of A2 compound

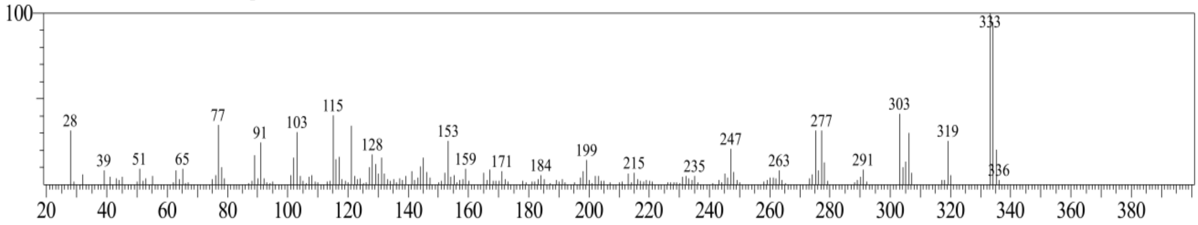


Figure 10. Mass spectra characterization results of A2 compound

Solvent Effectiveness of Synthesized (2E,6E)-bis(4-methoxybenzylidene) cyclohexanone and (E)-2-(4-methoxybenzylidene) cyclohexanone Compound

The selection of an efficient solvent in a reaction is essential because the solvent can interact with catalysts, substrates, and products so that it may increase or decrease the reaction rate and/or selectivity which has an impact on increasing or decreasing the yield of the product[42].

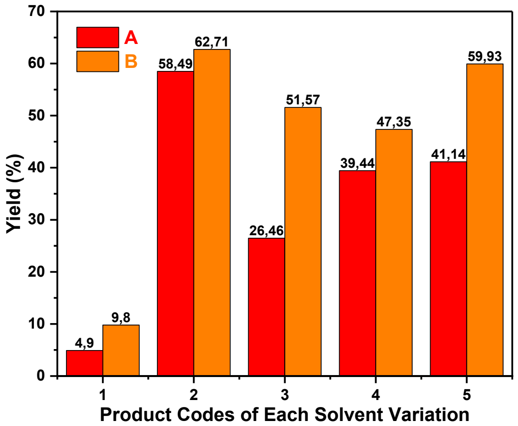


Figure 11. Comparison of solvent variation with % yield in compound A2 and B2

Based on the results shown in **Figure 11**, the solvent variation that resulted in the highest %yield in the synthesis of compounds (2E,6E)-bis(4-methoxybenzylidene) cyclohexanone and (E)-2-(4-methoxybenzylidene) cyclohexanone is H_2O/MeOH solvent (1:1 v/v). Aqueous-organic solvents, in particular, alcohol-water mixtures, are commonly suitable for synthesis and purification processes[43]. In previous studies, hydroalcoholic solvent systems, namely methanol-water, also gave the best yields compared to pure methanol or pure water solvents[11,42]. Mixed water-alcohol solvents or hydroalcoholic systems are widely used as an alternative to overcome the shortcomings of pure water or pure alcohol solvents. Solvents with hydroalcoholic systems (methanol-water) as the reaction medium can significantly improve stereocontrol and %yield in a shorter reaction time. In addition, the methanol-water mixture can facilitate the catalytic process as it provides homogeneous conditions in the aldol reaction[10]. The use of aqueous-organic solvent mixtures in Claisen-Schmidt condensation reaction can maximize reaction conditions, such as dissolving reactants and catalysts, and activating catalyst[9].

NaOH has low solubility in simple alcohol solvents, such as MeOH and EtOH, despite the presence of polar hydroxyl groups. This limited solubility arises from the nonpolar nature of the alkyl chains in these alcohols[44]. The solubility of polar catalysts like NaOH improves with the addition of H_2O, which promotes ionization to form hydroxide (OH^-) anions. Small anions with high charge density, like hydroxide, are stabilized by hydrogen bond formation in protic solvents[43]. The more hydrogen bonding interactions formed between polar solvents and NaOH, the more effectively the solvent can dissociate the Na^+ and OH^- ions in NaOH[45]. Using a more polar solvent can further weaken ionic interactions[46]. Polar solvents, in particular, are highly effective for dissolving anions due to their hydrogen-bonding capabilities. However, it is important to note that stronger solubilization can reduce the nucleophilic reactivity of anions[20]. Polar solvents dissolve both cations and anions efficiently through electrostatic interactions: δ^- atoms (e.g., oxygen) stabilize positive ions, while δ^+ atoms (e.g., hydrogen) stabilize negative ions[47]. In a hydroalcoholic solvent system, water aids in dissolving and activating the NaOH catalyst, where OH^- ions from NaOH help form enolate ions by attacking the α-hydrogen on cyclohexanone. The greater the availability of OH^- ions to interact with the α-hydrogen on cyclohexanone, the higher the yield of the product.

Simple alcohols in alcohol-water solvent mixtures can help dissolve less polar parts of molecules, such as cyclohexanone and 4-methoxybenzaldehyde. The aromatic groups that are found in 4-methoxybenzaldehyde are generally hydrophobic[48], while cyclohexanone contains a cyclic alkyl that tends to be more soluble in non-polar solvents, which reinforces the non-polar nature of cyclohexanone[49]. These characteristics make both starting materials difficult to dissolve in water. Therefore, to make the starting materials (cyclohexanone and 4-methoxybenzaldehyde) and catalyst (NaOH) mix completely, it is appropriate to use a hydroalcoholic solvent system based on the data in **Figure 11**.

Solvents also play an important role in the heat generation mechanism in reactions using microwave irradiation. The amount of microwave irradiation energy transfer depends on the dielectric properties of the molecule, such as the dielectric constant. Compounds with a high dielectric constant (polar) tend to absorb good microwave energy. Therefore, absorption and heating can be very selective with this method[50]. Since the starting materials, cyclohexanone and 4-methoxybenzaldehyde, are less polar, they cannot absorb microwave radiation well. To maximize reaction conditions using microwave irradiation, it is necessary to add a solvent that can help with heat distribution and microwave absorption.

Each solvent absorbs different microwave energy and can be categorized into three absorption abilities: low, medium, and high. Alcohol can absorb microwave radiation with high absorption ability, and water is categorized in the medium group[51,52]. The microwave energy absorption capacity of a material is proportional to the microwave penetration rate or in other words, the greater the microwave absorption capacity, the deeper the microwave is able to penetrate the material and produce heat. The order of microwave absorption capacity is ethanol > methanol > water[53]. The addition of small amounts of polar solvents such as H_2O or EtOH can cause significant coupling effects[51].

Based on the results shown in **Figure 11**, the solvent variation that facilitates the lowest %yield in the synthesis of compounds (2E,6E)-bis(4-methoxybenzylidene) cyclohexanone and (E)-2-(4-methoxybenzylidene) cyclohexanone is H_2O. The use of water in organic synthesis is only hindered by the low solubility of organic compounds at room temperature. The strategy to overcome the problem of hydrophobic effects is the use of water at high temperatures. The high temperature, near the critical point, can alter the properties of water that are observed at room temperature. High temperature near-critical water (NCW) exhibits attractive properties for organic synthesis applications. The dielectric constant of water changes from 78.5 at 25 °C to 27.5 at 250 °C (similar to acetonitrile at 25 °C) and 20 at 300 °C (similar to acetone at 25 °C). This means that at these temperatures, water can be considered as a quasi organic solvent[50]. However, due to the limitations of the microwave oven instrument used, which is not equipped with temperature and pressure controls, making the setting of reaction conditions limited. Therefore, there is a need for a microwave oven instrument equipped with temperature and pressure control in order to change the physical properties of water to dissolve less polar reactants.

UV Protector Activity

Based on **Figure 5**, the λ_{max} of the (2E,6E)-bis(4-methoxybenzylidene) cyclohexanone compound has 3 absorption peaks at λ 358.50 nm, which can provide protection against UV-A, and λ 243 nm and 206.50 nm can provide protection against UV-C. While the (E)-2-(4-methoxybenzylidene) cyclohexanone compound absorbs light at a maximum wavelength of λ 285 nm and λ 225 nm thus has the ability to protect against UV-C rays. The compound (2E,6E)-bis(4-methoxybenzylidene) cyclohexanone has a different type of protection depending on the concentration of the compound, where the maximum result is obtained at a concentration of 50 ppm with an SPF value of 9,908 therefore it is categorized as maximum protection. Meanwhile, the (E)-2-(4-methoxybenzylidene) cyclohexanone compound produced higher SPF values than the (2E,6E)-bis(4-methoxybenzylidene) cyclohexanone compound at each concentration. The best SPF value was obtained at the highest concentration of 50 ppm with a value of 15.324 and categorized as ultra protection. The higher SPF value in (E)-2-(4-methoxybenzylidene) cyclohexanone compound is due to the λ_{max} that is close to the UV-B region and this compound is suspected to still be a mixed compound. The SPF value of each concentration is shown in **Table 6**.

Table 6. SPF value of each concentration

Code	Concentration (ppm)	SPF Value	Protection Ability
A2	10	2.094	Minimal
	20	4.222	Moderate
	30	6.410	Extra
	40	8.326	Maximal
	50	9.908	Maximal
B2	10	3.062	Minimal
	20	6.362	Extra
	30	9.499	Maximal
	40	12.691	Maximal
	50	15.324	Ultra

According to **Table 6**, the increasing concentration of (2E,6E)-bis(4-methoxybenzylidene) cyclohexanone and (E)-2-(4-methoxybenzylidene) cyclohexanone results in higher SPF value. Both synthesized compounds have potential as sunscreen agents and were synthesized using environmentally friendly methods and materials. Based on the available literature at the time of writing, no studies have reported SPF testing for compounds with this exact chemical structure. Nevertheless, several compounds within the same structural class, *α,β*-unsaturated ketones, such as hexagamavunon-5 (HGV-5), a curcumin analog with the chemical structure 2,6-bis-(4-hydroxy-3,5-dimethoxybenzylidene) cyclohexanone, have been studied by Muhlida *et al.*,[54] show that HGV-5 compounds with concentrations of 200, 500, 1000, and 2000 ppm produced SPF values of 15.84, 37.75, 76.43, and 153.96, respectively. Wijayanti *et al.*,[55] reported that chalcone derivatives containing methoxy substituents showed that the addition of methoxy substituents to chalcone caused a red shift (bathochromic shift) with strong UV absorption and significant SPF values, indicating their potential as sunscreen agents. However, in order to be applied as sunscreen agents, the synthesized compounds must undergo a series of required testing stages to ensure safety, such as the permitted dose in its use for humans.

4. CONCLUSIONS

Two benzylidene cyclohexanone derivatives of (2E,6E)-bis(4-methoxybenzylidene) cyclohexanone (yellow needles) and (E)-2-(4-methoxybenzylidene) cyclohexanone (orange) were successfully synthesized. The H_2O/MeOH (1:1 v/v) solvent system proved to be the most effective, yielding 58.49% and

62.71% for each compound. The SPF values increased with compound concentration. The (2E,6E)-bis(4-methoxybenzylidene) cyclohexanone demonstrated a maximum SPF of 9.908, providing optimal protection at 50 ppm, while the (E)-2-(4-methoxybenzylidene) cyclohexanone compound reached a superior SPF of 15.324, categorized as ultra protection.

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