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Subject : Result of Review Manuscript ID No. 2015-08-830

Encl. : 2

Yogyakarta, 1 April 2016

Dear Ms. Sri Handayani,

Chemistry Education Department, Faculty of Mathematics and Natural Science, Yogyakarta State University

This is to acknowledge and inform you that the paper entitles:

Microwave-Assist Organic Reactions: Eco-friendly Synthesize of Benzilidenecyclohexanone Derivative

written by:

Sri Handayani, Cornelia Budimarwanti, and Winarto Haryadi

has been reviewed and could be published in *Indones. J. Chem.* after major revision. The author should make some correction as follows:

REVIEWER I:

1. The product of synthesis have been known. Please provide any physical properties like m.p or b.p, etc and give the comparation with literature
2. The procedure is clear enough. What kind the purification has been used.
3. The microwave that has been used is not clear enough. What is the series, power (watt?)
4. Synthesis using MW is usually discussing on variable of power in MW. How about this? Power (watt) is constant or variation power?
5. Since the used MW is kitchen microwaves, is radiation for 2 minutes continuous or intermittent
6. Please, add more recent references for under 5 years old relating to MW synthesis of Aldol condensation

REVIEWER II:

Abstract: Systematically and clearly rewrite your abstract

Introduction: You did not cite any important references related to the synthesis of your product. Please find in the attachment files.

Method:

- It is not quite clear
- Did you do NOESY analysis?
- Working up method?

Result and Discussion:

- You particularly discussed about the principle of MAOS, and you did not provide detail discussion on your synthesis
- Write the mechanism
- Is that isolated yield? How could you get 115% yield?
- In my opinion, you could not compare your results MAOS vs conventional heating, since you use the different system (solvent)
- Report the yield

References: Rewrite your references with Indones. J. Chem. Author's manual template

Please kindly send your revised manuscript by 16th April 2016, so that the article could be published in the upcoming *Indones. J. Chem.* Also **kindly send your response to the reviewers' comments (each point) in a separate letter**. Thank you for your submission and we are waiting for the other articles from you and your colleagues.

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Indonesian Journal of Chemistry

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Sincerely yours,

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2015-08-830

EVALUATION FORM
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Title	Microwave-Assist Organic Reactions: Eco-friendly synthesize of benzilidenecyclohexanone derivative
Date of receiving	20 August 2015

REVIEWER I

Please give this symbol (√) to mark your evaluation in the appropriate space

Criteria	Excellent	Good	Fair	Poor
Originality of the work			✓	
Scientific merit / Importance to field			✓	
Appropriateness of title. Does the title properly and clearly describe the paper? Too long? Too short?				✓
Is the abstract appropriate?			✓	
Are materials and methods described in clarity? No ambiguity?				✓
Is the mathematical formalism logical and clearly presented? (for theoretical work only)				
Description of experimental design				✓
Results presented in systematic and appropriate form?				✓
Statistical treatment of data? (if necessary)				
Relevance of discussion				✓
Soundness of interpretation and conclusions				✓
Appropriate literature citations. Are key references given?				✓
Quality of Figures			✓	
Clarity and style of tables			✓	
Article length (if too long. suggest ways to condense)			✓	
Overall quality of the paper				✓

Microwave-Assist Organic Reactions: Eco-friendly synthesize of benzilidenecyclohexanone derivative

ABSTRAK

The synthesis of dibenzilidenecyclohexanone derivatives by environmentally friendly MAOS aldol condensation had been carried out. The reaction was started by searching the optimum contentration of NaOH as catalyst. Condensation reaction was performed by reacting benzaldehyde or its derivative with cyclohexanone in microwave oven by mole ratio 2 : 1 with optimum concentration of NaOH as catalyst for 2 minutes duration. In this reaction we used aquadest and methanol as solvent. The reaction yield was determined by TLC scanner and the structure was elucidated by FTIR and NMR spectrometer. The synthesis of same compound was performed by stirring method as comparation. The research revealed that dibenzilidenecyclohexanone synthesis using MAOS is better than stirring method.

Keywords: ?

Telah dilakukan sintesis dibenzilidensikloheksanon dan turunannya melalui reaksi kondensasi aldol yang ramah lingkungan menggunakan metode MAOS. Reaksi diawali dengan optimasi konsentrasi natrium hidroksida sebagai katalis. Reaksi kondensasi dilakukan dengan cara mereaksikan benzaldehida atau turunannya dengan sikloheksanon dalam krus porselen dengan rasio mol 2:1 menggunakan katalis natrium hidroksida. Pelarut yang digunakan adalah aquades dan metanol. Krus ditutup dengan aluminium foil dan direaksikan menggunakan microwave selama 2 menit. Selanjutnya padatan hasil reaksi dianalisis menggunakan TLC dan TLC scanner untuk menentukan rendemennya. Elusidasi struktur dilakukan menggunakan FTIR dan NMR. Sebagai pembanding, dilakukan sintesis senyawa yang sama tetapi menggunakan metode stirring. Hasil riset membuktikan bahwa hasil sintesis dibenzilidensikloheksanon menggunakan metode MAOS lebih baik daripada metode stirring.

Keywords : dibenzilidensikloheksanon, MAOS, ramah lingkungan

Introduction.

Benzalacetone has a very interesting structure to be studied and developed. Several benzalacetone analogues have been reported as an active antioxidant [1, 2]. Active antioxidants compounds are expected to be a high potential anticancer candidate. In fact, one of dibenzalacetone derivative i.e 2,5-bis(4'-hydroxy-3',5'-dimethyl)-benzylidenecyclopenthanone or commonly known as the PGV-1 was reported to have the potential to inhibit the growth of tumors in T47D cells [3].

Some biological activities have been reported from analogue benzalacetone. (2E, 6E)-2.6-dibenzylidenecyclohexanone and E-2-benzylidenecyclohexanone are analogue of benzalacetone which can be synthesized using raw material cyclohexanone and benzaldehyde. Dibenzylidenecyclohexasanone and benzylidenecyclohexanone compounds are expected to have a biological activity similar to benzalacetone derivatives.

Modification of the synthesis process has to do to obtain optimum results. Some researchers have developed cross aldol condensation reaction with a variety of methods and catalysts. Several methods have been reported, among others, using the stirring [2], solvent free reaction [4], and ultrasonic-asisted method [5]. Synthesis vanilinacetone with stirring for 3 hours giving yield 13.06 to 94% [6]. Synthesis of dibenzalacetone's derivative through cross aldol condensation reaction without solvent conducted by Salehi *et al.* [7] give results between 82-98% with reaction time of 2-8 hours. While the synthesis of ultrasonic-asisted method with a reaction time of about 1.5 hours yield about 70 to 97% [5]. From the research, concluded that the highest yield is obtained when the synthesis of dibenzalacetone derivatives with double aldol condensation on both sides who have Hα. While the current yield of mono condensation on the one hand, is generally low. The results of the synthesis is always has dibenzalacetone as a byproduct of double condensation products.

Trends synthesis process today has shifted from the traditional concept that puts the maximum yield become eco-friendly processes that give more attention to the reaction process. Eco-friendly reaction process is a reaction that eliminate or reduce waste, save energy and avoid the use of toxic or hazardous compounds [8]. Based on these criteria, some researchers have conducted the synthesis of organic compounds using the method of Microwave Assisted Organic Synthesis (MAOS) [4, 9, 10]. The advantage via Maos reaction are the reaction of a cleaner, economical, environmentally friendly, can use microwave ovens household and only use simple glassware so easily taught to students [11].

From some literature, it is necessary to synthesis dibenzylidenecyclohexanone with eco-friendly methods. Synthesis was conducted by MAOS for 120 seconds using methanol as solvent. MAOS is the new method that expected to effectively reduce: reaction time, electrical energy use, harmful solvents and waste by reducing the catalyst.

EXPERIMENTAL SECTION

Materials

The materials used for the synthesis include benzaldehyde, 2-hidroxybenzaldehyde, 4-methoxybenzaldehyde, 3,4-dimethoxybenzaldehyde cyclohexanone, ethanol, sodium hydroxide, chloroform, hexane and aquades. All the ingredients from E-Merck.

Instrumentations

instruments are suggested to be split into several sentences according to the utilization

The equipment that used were TLC Scanner, Nicolet Avatar 360 FTIR and NMR spectrometer.

microwave ?

Procedure

Optimization of sodium hydroxide concentration. Sodium hydroxide (0.0025 mole) in 2 mL methanol was placed in a porcelain crucible. 4-methoxybenzaldehyde (0.01 mole) and cyclohexanone (0.005 mole) was added consecutively. Porcelain crucible was covered using aluminum foil and put in the microwave for 2 minutes. Reaction products were analyzed using TLC and TLC scanner to determine the yield. Repeat the same procedure using NaOH 0.005; 0.0075; 0.01 and 0.0125 mol

intermitte or continu

Synthesis of (2E, 6E) -2.6-dibenzylidenecyclohexanone (1) by MAOS. Sodium hydroxide (0.005 mole) was dissolved with 2 mL methanol in a porcelain crucible. Benzaldehyde (0.01 mole) and cyclohexanone (0.005 mole) was added. Porcelain crucible covered with aluminum foil and then put in a microwave oven for 2 minutes. The product was dried and weighed to determine the yield of the reaction. The results are then analyzed using TLC, TLC scanner, and then identified by FTIR and NMR spectrometer. Repeat the same procedure to synthesize (2E,6E)-2.6-bis(4-

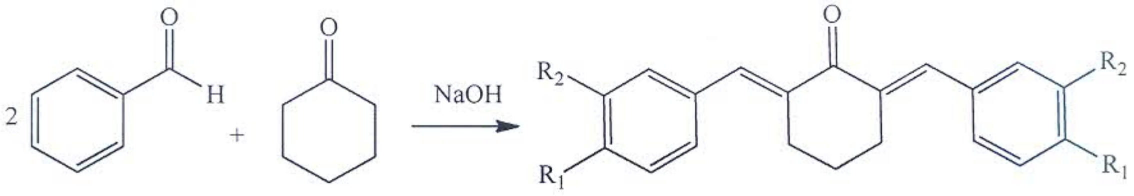
- heat
- time
- temp?

methoxybenzylidene)Cyclohexanone (**2**) and (2E,6E)-2.6-bis(3,4-dimethoxybenzylidene)Cyclohexanone (**3**).

Synthesis of compound 1 with stirring method. Sodium hydroxide (0.005 mole) dissolved in 2 mL of distilled water. Benzaldehyde (0.01 mole), cyclohexanone (0.005 mole) and 3 mL of ethanol was added to the solution. Stir the mixture at 10^0C for 120 minutes. Furthermore, let stand for 24 hours in the refrigerator until a precipitate is formed. Filter the precipitate and dried. Further analysis was performed the same as on the results of the synthesis using MAOS methods.) purification ?

RESULT AND DISCUSSION

Crossed aldol condensation of benzaldehyde and cyclohexanone is presented in Fig 1. Characterization of synthesized compounds **1**, **2** and **3** by using NMR spectrometer are listed in Table 1-3.

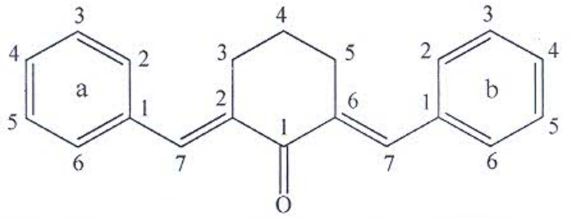


Compound 1 = R1 = R2 = H
Compound 2 = R1 = OCH3, R2 = H
Compound 3 = R1 = R2 = OCH3

Gambar 1. Crossed aldol condensation in synthesized compounds

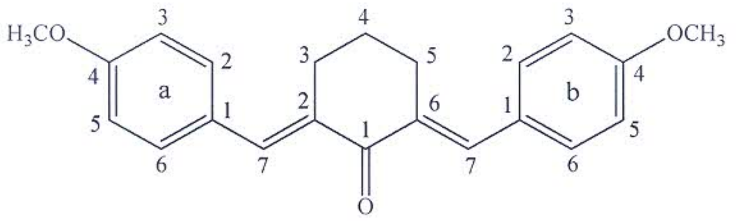
FTIR (KBr) (cm^{-1}) of compound **1**: 2926.27 (C-H stretching), 1604.77 (C=O), 1573 supported by 1488 (C=C aromatic), 1552.31 (C=C alkene). 1443 (CH_2 methylene). FTIR (KBr) (cm^{-1}) of compound **2**: 2938.52 (C-H stretching), 1594.67 (C=O), 1554.96 (C=C alkene), 1504.33 supported by 1416.16 (C=C aromatic), 1451.74 (CH_2 methylene), 1162.34-1112.72 (C-O), 843 (para subtitution). FTIR (KBr) (cm^{-1}) of compound **3**: 2930.57 (C-H stretching), 1596.84 (C=O), 1513.57 (C=C aromatic), 1451 (CH_2 methylene), 1250.77-1139.4 (C-O), 847 (para subtitution) [12].

Table 1. NMR (^{1}H and ^{13}C) of compound 1 (CDCl$_3$)



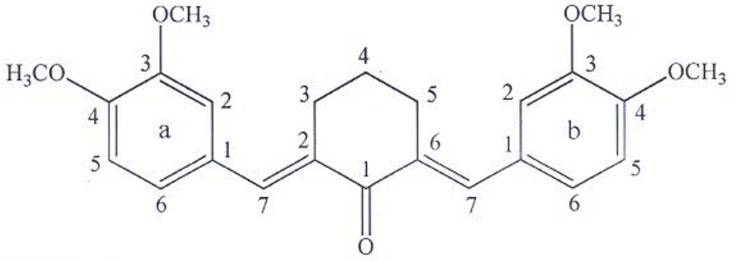
No C	δ (∑H, m, *J* Hz) ppm	δ C (ppm)
1	-	190.3
2,6	-	136.1
3,5	2.9 (4H, m, -)	28.4
4	1.8 (2H, m, -)	23
7	7.8 (2H, s, -)	136.9
1a,1b	-	135.9
2a,6a,2b,6b	7.46 (4H, d, 7.2)	130.3
3a,5a,3b,5b	7.4 (4H, t, 7.2)	128.3
4a,4b	7.3 (2H, d, 7.2)	128.5

Table 2. NMR (^{1}H and ^{13}C) of compound 2 (CDCl$_3$)



No C	δ (∑H, m, *J* Hz) ppm	δ C (ppm)
1	-	190.2
2,6	-	134.3
3,5	2.9 (4H, t, -)	28.5
4	1.8 (2H, m, -)	23
7	7.7 (2H, s, -)	136
1a,1b	-	128.7
2a,6a,2b,6b	7.45 (4H, d, 7.2)	132.2
3a,5a,3b,5b	6.9 (4H, d, 7.2)	113.8
4a, 4b	-	159.9
4a-OCH$_3$, 4b-OCH$_3$	3.8 (6H, s, -)	55.3

Table 3. NMR (^1H and ^{13}C) of compound 3 ($CDCl_3$)



No C	δ (∑H, m, *J* Hz) ppm	δ C (ppm)
1	-	190
2,6	-	136
3,5	2.9 (4H, t, -)	28.5
4	1.8 (2H, m, -)	23
7	7.7 (2H, s, -)	134
1a,1b	-	128
2a,2b	7.02 (2H, s, 7.2)	113
3a,3b	-	149
3a-OCH_3, 3b-OCH_3	3.91 (6H, s, -)	55
4a,4b	-	148
4a-OCH_3, 4b-OCH_3	3.92 (6H, s, -)	55
5a, 5b	6.9 (2H, d, 8.3)	110.8
6a, 6b	7.1 (2H, d, 8.3)	123.8

The benzylidenecyclohexanone synthesis begins with the optimization concentration of catalyst. It aims to determine the minimum concentration of catalyst to produce the maximum product. Results of optimization of catalyst concentrations are presented in Figure 2.

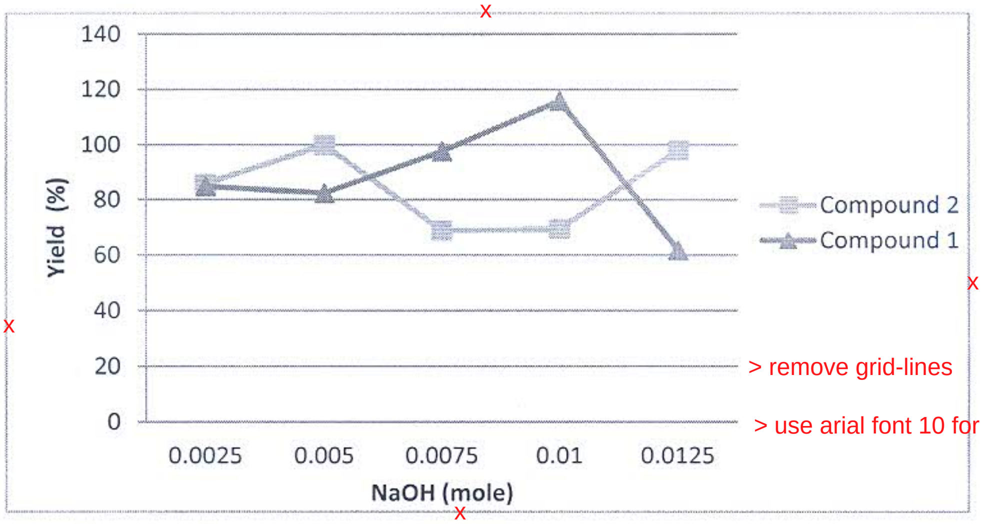


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Figure 2. Optimization of NaOH catalyst with MAOS method

NaOH optimum for the synthesis of compound **2** (0.005 mole cyclohexanone, 4-methoxybenzaldehyde 0.01 mole) was 0.005 mole which produces 100% yield. These results indicate that minimum number of moles have produced maximum results. In the synthesis of compound **1**, the highest yield of 115% was obtained at 0.01 mole NaOH, while NaOH 97.76% yield obtained at 0.0075 mole. Therefore, for the synthesis of compound **1**, the use of NaOH 0.0075 mol is more eco-friendly. This is consistent with one of green chemistry pillars, which use a minimum chemicals and reducing waste bases residu.

As a comparator, the stirring method was used to determine the effectiveness MAOS in the synthesis of dibenzylidenecyclohexanone. Moles number of raw materials and catalysts that used are the same. Comparison of the results using MAOS and stirring method is presented in Figure 3.

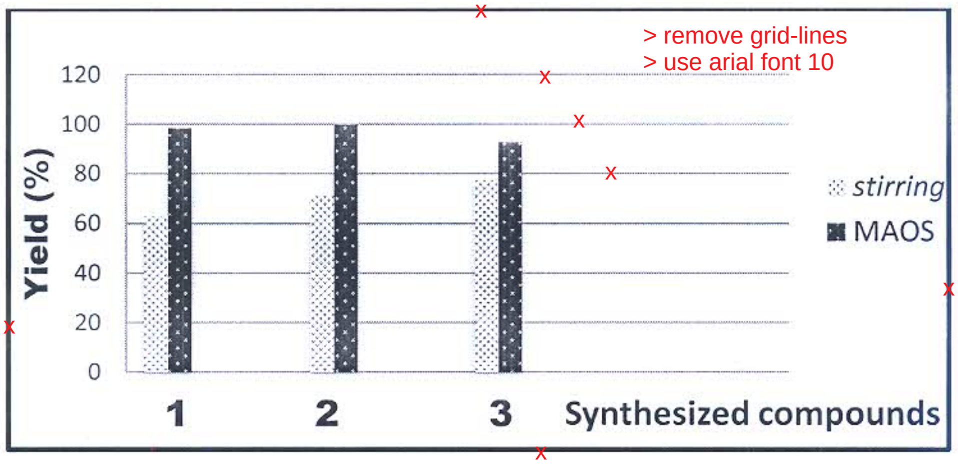

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Figure 3. Comparison of the results using MAOS and stirring method

Eco-friendly synthesis process is a chemical reaction using efficiently raw material, less waste, avoid toxic chemicals and a short reaction time [13]. Based on these conditions, synthesis dibenzylidenecyclohexanone was done using MAOS methods. MAOS has several advantages compared with conventional heating methods. In the conventional method of heating, the reaction container is heated and then transfer heat into the reaction system by convection process. Thus this process takes a long time and high energy. Heating with microwave is more efficient in terms of energy, homogen temperature and faster until at high temperatures. So the main advantage of using the microwave is a very short reaction time and high yield [14].

The tools that used in this method is domestic microwave oven. Opinion of Some reseachers is that domestic microwave oven has a disadvantage in terms of temperature control and low reproducibility. If using a solvent which has a low boiling point, can lead to over heated during the reaction. Over pressure can also occur when using a closed reaction system. To avoid over-pressure and over-heated, the crucible porcelain that used was covered with aluminum foil. In this study, solvent that used is methanol because in addition to a high enough boiling point, heating using microwave oven require polar solvents. Dielectric polarization dipoles depends on the ability to adjusting the direction of the electric field applied. Seems to make sense to believe that the more polar solvent (with a high dielectric constant), the more rapidly the radiation is absorbed so that the higher the temperature obtained [15].

The data in Figure 3 shows that the yield of the synthesis using MAOS larger than the stirring method. Advantages of MAOS is highly reduce reaction time, increase of yields and product purities to enhance conventionally procces experiments. Very rapid heating on high temperature on MAOS occur based on the implementation of the Arrhenius law. Temperature changes that usually takes a few hours at reflux temperature, to be perfect in just a few minutes using microwave. The rapid heating experienced in microwave-assisted transformations also lead to changed product distributions compared to a conventional method if the reaction product distribution is controlled by complex temperature-dependent kinetic profiles. This could clarify why microwave-assisted reactions performed at an optimized reaction temperature have been establish to be cleaner, guiding to less by-products compared to the conventionally method [16].

Cross aldol condensation reaction is usually performed using a conventional stirring method for a few hours and should left to stand over night. It also requires amount of solvent. The results also still contains residual catalysts and solvents. So conventional method requires high energy for stirring and heating also unwise use of chemicals.

Conclussion

The conclusion from this study is dibenzylidenecyclohexanone and its derivatives can be synthesized by the reaction Claisen-Scmidth using MAOS. Synthesized process using MAOS is better than stirring method. Based on this research, it can be seen that the product of MAOS synthesis takes very short time reaction, short synthesis flow, almost no waste and higher yield.

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Date of receiving	20 August 2015

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Criteria	Excellent	Good	Fair	Poor
Originality of the work				✓
Scientific merit / Importance to field			✓	
Appropriateness of title. Does the title properly and clearly describe the paper? Too long? Too short?		✓		
Is the abstract appropriate?				✓
Are materials and methods described in clarity? No ambiguity?				✓
Is the mathematical formalism logical and clearly presented? (for theoretical work only)	–	–	–	–
Description of experimental design			✓	
Results presented in systematic and appropriate form?			✓	
Statistical treatment of data? (if necessary)	–	–	–	–
Relevance of discussion				✓
Soundness of interpretation and conclusions				✓
Appropriate literature citations. Are key references given?				✓
Quality of Figures		✓		
Clarity and style of tables		✓		
Article length (if too long. suggest ways to condense)			✓	
Overall quality of the paper				✓

Rewrite your abstract!!!

Microwave-Assist ed Organic Reactions: Eco-friendly ~~synthesize~~ synthesis of benzilidenecyclohexanone derivative s

y.

(*) The condensation reaction was performed by reacting benzaldehyde or its derivatives and cyclohexanone in the presence of NaOH as catalyst for 2 min in microwave oven. The study was commenced by searching the optimum ~~concentra~~ concentration of NaOH as catalyst.

(*) Which kind of aldehyde that you used.

(*) Report the yield.

(*) For the comparison, the reaction was also carried out by stirring method.

ABSTRAK

COMMENCED ?

The synthesis of dibenzilidenecyclohexanone derivatives by environmentally friendly MAOS aldol condensation had been carried out. The reaction was ~~started~~ by searching the optimum contentration of NaOH as catalyst. The Condensation reaction was performed by reacting benzaldehyde or its derivative ~~with~~ and cyclohexanone in microwave oven by mole ratio 2 : 1 with optimum concentration of NaOH as catalyst for 2 minutes duration. ~~In this reaction we used aquadest and methanol as solvent~~. The reaction yield was determined by TLC scanner and the structure was elucidated by FTIR and NMR spectrometer s. The synthesis of same compound was performed by stirring method as comparation. The research ~~revealed that~~ showed dibenzilidenecyclohexanone synthesis using of MAOS ~~is~~ was better than stirring method.

what is the base of the conclusion

keywords :

Telah dilakukan sintesis dibenzilidensikloheksanon dan turunannya melalui reaksi kondensasi aldol yang ramah lingkungan menggunakan metode MAOS. Reaksi diawali dengan optimasi konsentrasi natrium hidroksida sebagai katalis. Reaksi kondensasi dilakukan dengan cara mereaksikan benzaldehida atau turunannya dengan sikloheksanon dalam krus porselen dengan rasio mol 2:1 menggunakan katalis natrium hidroksida. Pelarut yang digunakan adalah aquades dan metanol. Krus ditutup dengan aluminium foil dan direaksikan menggunakan microwave selama 2 menit. Selanjutnya padatan hasil reaksi dianalisis menggunakan TLC dan TLC scanner untuk menentukan rendemennya. Elusidasi struktur dilakukan menggunakan FTIR dan NMR. Sebagai pembanding, dilakukan sintesis senyawa yang sama tetapi menggunakan metode stirring. Hasil riset membuktikan bahwa hasil sintesis dibenzilidensikloheksanon menggunakan metode MAOS lebih baik daripada metode stirring.

Kata Kunci.
~~Keywords~~ : dibenzilidensikloheksanon, a MAOS, ramah lingkungan

IT IS BETTER TO DRAW THE STRUCTURE OF PGV-1 and THE compound you would LIKE TO SYNTHESIZE!

E OR Z = ITALIC

Rewrite with THE order 1, 2, 3.

Introduction.

① Benzalacetone has a very interesting structure to ~~be studied~~ study and ~~developed~~ develop. Several benzalacetone analogues have been reported as an active antioxidant [1, 2]. Active antioxidants compounds are expected to be a high potential anticancer candidate. In fact, one of dibenzalacetone derivative i.e, 2,5-bis(4'-hydroxy-3',5'-dimethyl)-benzylidenecyclopenthanone or commonly known as the PGV-1 was reported to have the potential to inhibit the growth of tumors in T47D cells [3]. mention THE Biological activities!

② * Some biological activities have been reported from analogue benzalacetone. FROM THE synthetic point of view, ④ (2E,6E)-2,6-dibenzylidenecyclohexanone and E-2-benzylidenecyclohexanone are analogues of benzalacetone which can be synthesized using raw material of cyclohexanone and benzaldehyde via cross aldol reaction. ③ Dibenzylidenecyclohexasanone and benzylidenecyclohexanone compounds ~~are~~ were expected to have ~~a~~ biological activities similar to benzalacetone derivatives.

~~Modification of the synthesis process has to do to obtain optimum results.~~ Some researchers have developed cross aldol condensation reaction with a variety of methods and catalysts. Several methods have been reported, ~~among others~~ such as, using the stirring [2], solvent free reaction [4], and ultrasonic-asisted method [5]. Synthesis of vanilinacetone derivatives with stirring for 3 hours ~~giving~~ gave the yield from 13.06 to 94% [6]. Solvent-free synthesis of dibenzalacetone derivative ~~through~~ via cross aldol condensation reaction ~~without solvent~~ was conducted by Salehi *et al.* [7] and ~~give~~ gave results between 82-98% yield with reaction time of 2-8 hours. While the synthesis of ultrasonic-asisted method with a reaction time of about 1.5 hours yield about 70 to 97% [5]. From the research, concluded that the highest yield is obtained when the synthesis of dibenzalacetone derivatives with double aldol condensation on both sides who have Hα. While the current yield of mono condensation on the one hand, is generally low. The results of the synthesis is always has dibenzalacetone as a byproduct of double condensation ~~products~~.

please explain THE studies on THE variation of catalyst!

WHAT was THE compound in THIS method?

Refference!

contradiction!

Trends synthe~~sis~~tic process today has shifted from the traditional concept that puts the maximum yield become eco-friendly processes that give more attention to the reaction process. Eco-friendly reaction process is a reaction ~~that~~ which eliminate or reduce waste, save energy and avoid the use of toxic or hazardous compounds [8]. Based on these criteria, ~~some~~ several researchers have conducted the synthesis of organic compounds using the method of Microwave Assisted Organic Synthesis (MAOS) [4, 9, 10]. The

WHICH organic compound.

according to the literature study, we would like to develop

MAOS. rapid,

advantage via ~~Maos~~ reaction are ~~the reaction of a~~ cleaner, economical, environmentally friendly, IT can use microwave ovens household and Require ~~only use~~ simple glassware and. ~~so~~ easily taught to students [11].

From some literature, it is necessary to synthesis dibenzylidenecyclohexanone with eco-friendly methods. Synthesis was conducted by MAOS for 120 seconds using methanol as solvent. MAOS is the new method ~~that~~ which is expected to effectively reduce reaction time, electrical energy use, harmful solvents and waste by reducing the catalyst. ?

EXPERIMENTAL SECTION

Materials

The materials used for the synthesis include benzaldehyde, 2-hidroxybenzaldehyde, 4-methoxybenzaldehyde, 3,4-dimethoxybenzaldehyde cyclohexanone, ethanol, sodium hydroxide, chloroform, hexane and aquades. All the ingredients were purchased from ~~E-Merck~~. methanol ?

you did not use it!

Instrumentations

The equipment that used were TLC Scanner, Nicolet Avatar 360 FTIR and NMR spectrometer. specifications? microwave ?

Procedure

(PLEASE USE ALSO THE NUMBER OF EQUIVALENT FOR EACH CHEMICAL!)

Optimization of sodium hydroxide concentration. Sodium hydroxide (0.0025 mole) in 2 mL methanol was placed in a porcelain crucible. 4-Methoxybenzaldehyde (0.01 mole) and cyclohexanone (0.005 mole) was added consecutively. Porcelain crucible was covered using aluminum foil and ~~put~~ Heated in the microwave for 2 minutes. Reaction products were analyzed using TLC and TLC scanner to determine the yield. ~~Repeat~~ the same procedure was repeated using different concentration of NaOH using NaOH 0.005; 0.0075; 0.01 and 0.0125 mol ? mmol!

CONVERT TO mmol!

Synthesis of (2E, 6E) -2.6-dibenzylidenecyclohexanone (1) by MAOS. Sodium hydroxide (0.005 mole) was dissolved with 2 mL methanol in a porcelain crucible. Benzaldehyde (0.01 mole) and cyclohexanone (0.005 mole) was added. Porcelain crucible covered with aluminum foil and then ~~put~~ Heated in a microwave oven for 2 minutes. The product was dried and weighed to determine the yield of the reaction. The ~~results are~~ product was then analyzed using TLC, TLC scanner, and ~~then~~ identified by FTIR and NMR spectrometers. ~~Repeat the same procedure to synthesize (2E,6E)-2.6-bis(4-~~

~~THE similar procedure was carried out for 4 methoxy benzaldehyde,~~ ...

PLEASE CLEARLY DESCRIBE THE WORK UP METHOD!

TEMPERATURE? Rf?

THE CONDITION IS TOTally different WITH THAT OF MAOS. IT COULD NOT BE used as THE comparison.

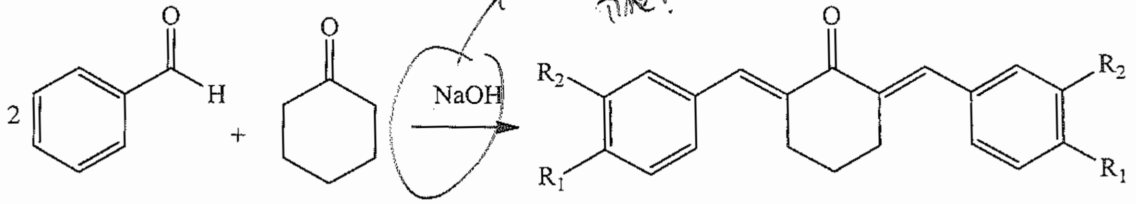
~~methoxybenzylidene)Cyclohexanone (2) and (2E,6E)-2.6-bis(3,4-dimethoxybenzylidene)Cyclohexanone (3).~~

Synthesis of compound 1 with stirring method. Sodium hydroxide (0.005 mole) dissolved in 2 mL of distilled water. Benzaldehyde (0.01 mole), cyclohexanone (0.005 mole) and 3 mL of ethanol was added to the solution. Stir the mixture at 10^{0}C for 120 minutes. Furthermore, let stand for 24 hours in the refrigerator until a precipitate is formed. Filter the precipitate and dried. Further analysis was performed the same as on the results of the synthesis using MAOS methods.

RESULT AND DISCUSSION

Cross~~ed~~ aldol condensation of benzaldehyde and cyclohexanone is presented in Fig 1. Characterization of synthesized compounds **1**, **2** and **3** by using NMR spectrometer are listed in Table 1-3.

solvent? temperature?, microwave condition? Time?



~~Compound~~ 1 = R1 = R2 = H
~~Compound~~ 2 = R1 = OCH3; R2 = H
~~Compound~~ 3 = R1 = R2 = OCH3

Gambar 1. Cross~~ed~~ aldol condensation in ~~synthesized compounds~~ of Benzaldehyde derivatives and cyclohexanone

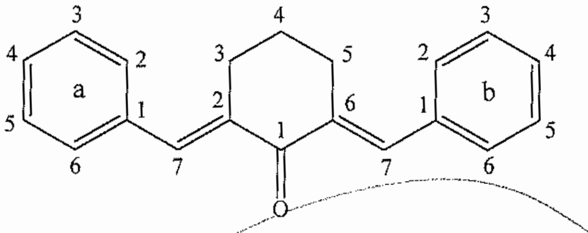
FTIR (KBr) (cm^{-1}) of compound **1**: 2926.2~~7~~ (C-H stretching), 1604.7~~7~~ (C=O), 1573 supported by 1488 (C=C aromatic), 1552.~~31~~ (C=C alkene). 1443 (CH_2 methylene). FTIR (KBr) (cm^{-1}) of compound **2**: 2938.~~52~~ (C-H stretching), 1594.~~67~~ (C=O), 1554.~~9~~6 (C=C alkene), 1504.3~~9~~ supported by 1416.~~8~~6 (C=C aromatic), 1451.~~74~~ (CH_2 methylene), 1162.~~34~~-1112.~~72~~ (C-O), 843 (para subtitution). FTIR (KBr) (cm^{-1}) of compound **3**: 2930.~~57~~ (C-H stretching), 1596.8~~4~~ (C=O), 1513.~~57~~ (C=C aromatic), 1451 (CH_2 methylene), 1250.7~~9~~-1139.~~4~~ (C-O), 847 (para subtitution) [12].

put them in the experimental part!

you did not explain the scientific reasons why did you use NaOH and cyclohexanone in your study.

- Please explain how the NMR data could show that the reaction has taken place.!
- Please show that the configuration of double bonds are (E)!

Table 1. NMR (^1H and ^{13}C) of compound 1 ($CDCl_3$)

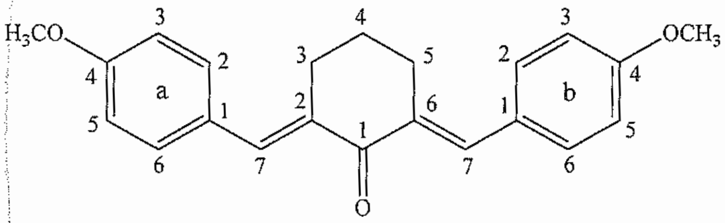


No C	δ (∑H, m, *J* Hz) ppm	δ C (ppm)
1	-	190.3
2,6	-	136.1
3,5	2.9 (4H, m, -)	28.4
4	1.8 (2H, m, -)	23
7	7.8 (2H, s, -)	136.9
1a,1b	-	135.9
2a,6a,2b,6b	7.46 (4H, d, 7.2)	130.3
3a,5a,3b,5b	7.4 (4H, t, 7.2)	128.3
4a,4b	7.3 (2H, d, 7.2)	128.5

Two shift after the point

one shift after the point

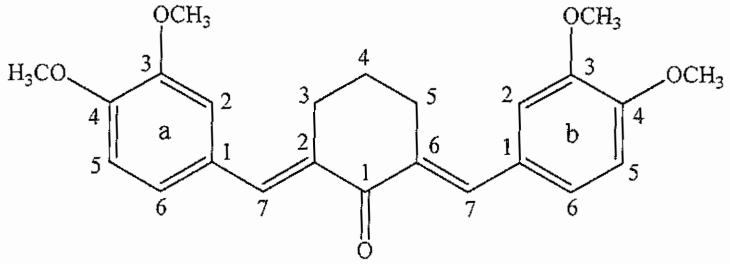
Table 2. NMR (^1H and ^{13}C) of compound 2 ($CDCl_3$)



No C	δ (∑H, m, *J* Hz) ppm	δ C (ppm)
1	-	190.2
2,6	-	134.3
3,5	2.9 (4H, t, -)	28.5
4	1.8 (2H, m, -)	23
7	7.7 (2H, s, -)	136
1a,1b	-	128.7
2a,6a,2b,6b	7.45 (4H, d, 7.2)	132.2
3a,5a,3b,5b	6.9 (4H, d, 7.2)	113.8
4a, 4b	-	159.9
4a-OCH_3, 4b-OCH_3	3.8 (6H, s, -)	55.3

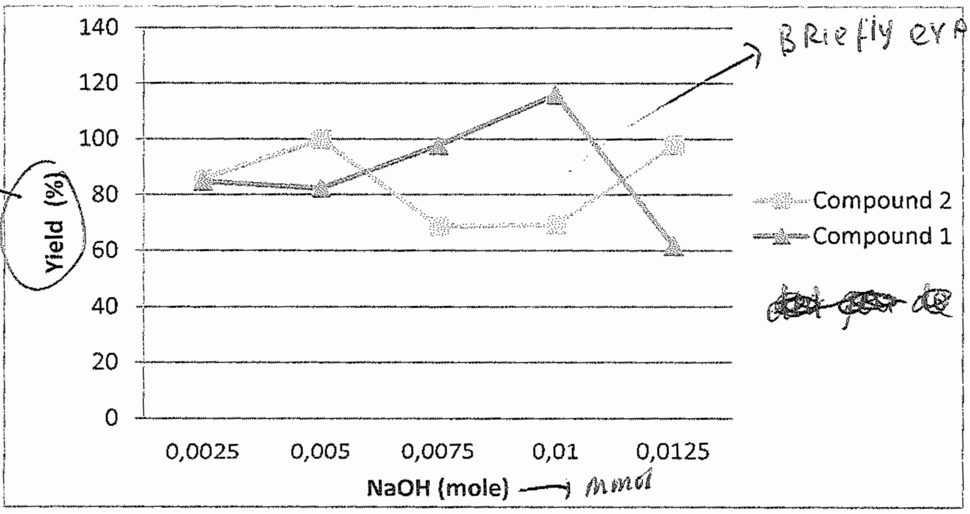
J = ?

Table 3. NMR (^{1}H and ^{13}C) of compound 3 ($CDCl_3$)



No C	δ (∑H, m, J Hz) ppm	δ C (ppm)
1	-	190
2,6	-	136
3,5	2.9 (4H, t, -)	28.5
4	1.8 (2H, m, -)	23
7	7.7 (2H, s, -)	134
1a,1b	-	128
2a,2b	7.02 (2H, s, 7.2)	113
3a,3b	-	149
3a-OCH_3, 3b-OCH_3	3.91 (6H, s, -)	55
4a,4b	-	148
4a-OCH_3, 4b-OCH_3	3.92 (6H, s, -)	55
5a, 5b	6.9 (2H, d, 8.3)	110.8
6a, 6b	7.1 (2H, d, 8.3)	123.8

The benzylidenecyclohexanone synthesis begins with the optimization concentration of catalyst. It aims to determine the minimum concentration of catalyst to produce the maximum product. Results of optimization of catalyst concentrations are presented in Figure 2.



are they "isolated yield"?

Briefly explain the trend!

the

→ mmol

Figure 2. Optimization of NaOH catalyst with MAOS method

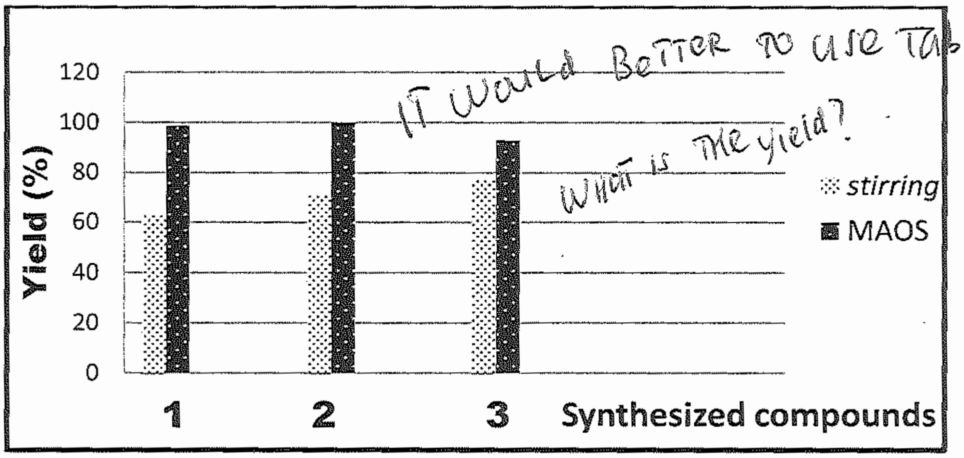
In the optimisation of a reaction, normally we choose one compound as a representatif for example Benzaldehyde. Then we optimize the concentration of NaOH. From the optimisation, you will find the optimum concentration of NaOH. With the optimum concentration in your hand, you will use <u>this concentration</u> for other Benzaldehyde derivatives. you are not necessary to do the optimisation for compound 1 and 2.

How come?

NaOH optimum for the synthesis of compound 2 (0.005 mole cyclohexanone, 4-methoxybenzaldehyde 0.01 mole) was 0.005 mole which produces 100% yield. These results indicated that minimum number of moles have produced ~~maximum~~ optimum results. In the synthesis of compound 1, the highest yield of 115% was obtained at 0.01 mole NaOH, while NaOH 97.76% yield obtained at 0.0075 mole. Therefore, for the synthesis of compound 1, the use of NaOH 0.0075 mol is more eco-friendly This is consistent with one of green chemistry pillars, which use ~~a minimum~~ chemicals and reducing waste bases residu.

not the appropriate term.

For the comparison ~~As a comparator~~, the stirring method was used to determine the effectiveness MAOS in the synthesis of dibenzylidenecyclohexanone. Moles number of raw materials and catalysts that used ~~are~~ were the same. Comparison of the results using MAOS and stirring method ~~is~~ was presented in Figure 3. you should use the same condition (solvent).



It would better to use table.

What is the yield?

Figure 3. Comparison of the results using MAOS and stirring method

Eco-friendly synthesis process is a chemical reaction using efficiently raw material, less waste, avoid toxic chemicals and a short reaction time [13]. Based on these conditions, synthesis dibenzylidenecyclohexanone was done using MAOS methods. MAOS has several advantages compared with conventional heating methods. In the conventional method of heating, the reaction container is heated and then transfer heat into the reaction system by convection process. Thus this process takes a long time and high energy. Heating with microwave is more efficient in terms of energy, homogeneous temperature and faster until at high temperatures. So the main advantage of using the microwave is a very short reaction time and high yield [14].

Methanol is not "eco-friendly"!

The tools that used in this method is domestic microwave oven. Opinion of Some reseachers is that domestic microwave oven has a disadvantage in terms of temperature control and low reproducibility. If using a solvent which has a low boiling point, can lead to over heated during the reaction. Over pressure can also occur when using a closed reaction system. To avoid over-pressure and over-heated, the crucible porcelain that used was covered with aluminum foil. In this study, solvent that used is methanol because in addition to a high enough boiling point, heating using microwave oven require polar solvents. Dielectric polarization dipoles depends on the ability to adjusting the direction of the electric field applied. Seems to make sense to believe that the more polar solvent (with a high dielectric constant), the more rapidly the radiation is absorbed so that the higher the temperature obtained [15].

The data in Figure 3 shows that the yield of the synthesis using MAOS larger than the stirring method. Advantages of MAOS is highly reduce reaction time, increase of yields and product purities to enhance conventionally procces experiments. Very rapid heating on high temperature on MAOS occur based on the implementation of the Arrhenius law. Temperature changes that usually takes a few hours at reflux temperature, to be perfect in just a few minutes using microwave. The rapid heating experienced in microwave-assisted transformations also lead to changed product distributions compared to a conventional method if the reaction product distribution is controlled by complex temperature-dependent kinetic profiles. This could clarify why microwave-assisted reactions performed at an optimized reaction temperature have been establish to be cleaner, guiding to less by-products compared to the conventionally method [16].

Cross aldol condensation reaction is usually performed using a conventional stirring method for a few hours and should left to stand over night. It also requires amount of solvent. The ~~results also still contains residual~~ catalysts ~~and solvents~~. So conventional method requires high energy for stirring and heating a~~lso unwise use of chemi~~cals.

High or less ?

Conclussion

The conclusion from this study is dibenzylidenecyclohexanone and its derivatives can be synthesized by the reaction Claisen-Scmidth using MAOS. Synthesized process using MAOS is better than stirring method. Based on this research, it can be should ~~seen~~ that the product of MAOS synthesis takes very short time reaction, short synthesis flow, almost no waste and higher yield.

What do you mean?

You did not explain it in the discussion.

In term of what?

Rewrite The Refferences Based On I2C Templater!

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The name of journal!

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what is it?

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Kepada: ijc@ugm.ac.id
Cc: handayani@uny.ac.id
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Dear Editor,
I sent my revision in the attachment file.
I'm sorry for the late revision.

Regards
Sri Handayani
Chemistry Education Department

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> Subject : Result of Review Manuscript ID No. 2015-08-830
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> Dear Ms. Sri Handayani,
> Chemistry Education Department, Faculty of Mathematics and Natural Science, Yogyakarta State University
>
> This is to acknowledge and inform you that the paper entitles:
>
> **Microwave-Assist Organic Reactions: Eco-friendly Synthesize of Benzilidenecyclohexanone Derivative**
>
> written by:
>
> ***Sri Handayani, Cornelia Budimarwanti, and Winarto Haryadi***
>
> has been reviewed and could be published in *Indones. J. Chem.* after major revision. The author should make some correction as follows:
>
> REVIEWER I:
> 1. The product of synthesis have been known. Please provide any physical properties like m.p or b.p, etc and give the comparation with literature
> 2. The procedure is clear enough. What kind the purification has been used.
> 3. The microwave that has been used is not clear enough. What is the series, power (watt?)
> 4. Synthesis using MW is usually discussing on variable of power in MW. How about this? Power (watt) is constant or variation power?
> 5. Since the used MW is kitchen microwaves, is radiation for 2 minutes continuous or intermittent
> 6. Please, add more recent references for under 5 years old relating to MW synthesis of Aldol condensation
>
> REVIEWER II:
> Abstract: Systematically and clearly rewrite your abstract
> Introduction: You did not cite any important references related to the synthesis of your product. Please find in the attachment files.
> Method:
> - It is not quite clear

> - Did you do NOESY analysis?
> - Working up method?
>
> Result and Discussion:
>
> - You particularly discussed about the principle of MAOS, and you did not provide detail discussion on your synthesis
> - Write the mechanism
> - Is that isolated yield? How could you get 115% yield?
> - In my opinion, you could not compare your results MAOS vs conventional heating, since you use the different system (solvent)
> - Report the yield
>
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Microwave-Assisted Organic Reactions: Eco-friendly synthesis of dibenzylidenecyclohexanone derivatives

Sri Handayani[1*], Cornelia Budimarwanti[1], Winarto Haryadi[2]

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*handayani@uny.ac.id

ABSTRAK

*The synthesis of dibenzylidenecyclohexanone derivatives through environmentally friendly MAOS (Microwave Assisted Organic Synthesis) aldol condensation had been carried out. The condensation reaction to synthesis the dibenzylidenecyclohexanone (**1**) was performed by reacting benzaldehyde and cyclohexanone in a mole ratio of 2:1 with NaOH as catalyst for 2 minutes in microwave oven. Benzaldehyde derivatives that had been used were 4-methoxybenzaldehyde and 3,4-dimethoxybenzaldehyde to synthesis of* (2*E*,6*E*)-2.6-bis(4-methoxybenzylidene)cyclohexanone (**2**) and (2*E*,6*E*)-2.6-bis(3,4-dimethoxybenzylidene)cyclohexanone (**3**). *The study was commenced by searching the optimum concentration of NaOH. The reaction yield was determined by TLC scanner and the structure was elucidated by FTIR and NMR spectrometer. For the comparison, the reaction was also carried out by stirring method. The optimum concentration of NaOH was obtained at 5 mmole. The yields of compound **1**, **2** and **3** synthesized via MAOS method are 98.62; 100 and 93%, respectively. The research also showed that synthesis of dibenzylidenecyclohexanone and its derivatives using MAOS is better than stirring method.*

Keywords : dibenzylidenecyclohexanone, MAOS, eco-friendly

Telah dilakukan sintesis dibenzilidensikloheksanon dan turunannya melalui reaksi kondensasi aldol yang ramah lingkungan menggunakan metode MAOS. Sintesis dibenzilidensikloheksanon (**1**) dilakukan melalui reaksi kondensasi antara benzaldehida dan sikloheksanon dalam krus porselen dengan rasio mol 2:1 menggunakan katalis natrium hidroksida selama 2 menit di dalam microwave. Turunan benzaldehida yang digunakan adalah 4-metoksibenzaldehida dan 3,4-dimetoksibenzaldehida untuk mensintesis (2*E*,6*E*)-2.6-bis(4-metoksibenziliden)sikloheksanon (**2**) dan (2*E*,6*E*)-2.6-bis(3,4-dimetoksibenziliden)sikloheksanon (**3**). Reaksi dimulai dengan mencari konsentrasi NaOH optimum sebagai katalis. Selanjutnya padatan hasil reaksi dianalisis menggunakan TLC dan TLC scanner untuk menentukan rendemennya. Elusidasi struktur dilakukan menggunakan FTIR dan NMR. Sebagai pembanding, dilakukan sintesis senyawa yang sama tetapi menggunakan metode stirring. Konsentrasi NaOH optimum diperoleh pada 5 mmol. Rendemen hasil sintesis senyawa **1, 2**, dan **3** berturut0turut sebesar 98,62; 100 dan 93%. Hasil riset membuktikan bahwa hasil sintesis dibenzilidensikloheksanon menggunakan metode MAOS lebih baik daripada metode stirring.

Kata kunci : dibenzilidensikloheksanon, MAOS, ramah lingkungan

Introduction.

Benzalacetone has a very interesting structure for being studied and developed. Several benzalacetone analogues have been reported as an active antioxidant [1, 2, 3, 4], antimutagenic [5], and anti-tubercular agent [6]. Active antioxidants compounds are expected to have a high potential anticancer candidate. One of dibenzalacetone derivatives is 2,5-bis(4'-hydroxy-3',5'-dimethyl)-benzylidenecyclopenthanone or is commonly known as the PGV-1, which shown in Fig.1. It was reported for having potential inhibition to the growth of tumors in T47D cells [7]. Dibenzylidenecyclohexanone and benzylidenecyclohexanone compounds are expected to have a similarity biological activities to benzalacetone derivatives. (2*E*, 6*E*)-2.6-dibenzylidenecyclohexanone and *E*-2-benzylidenecyclohexanone are analogue of benzalacetone which can be synthesized using raw material of cyclohexanone and benzaldehyde.

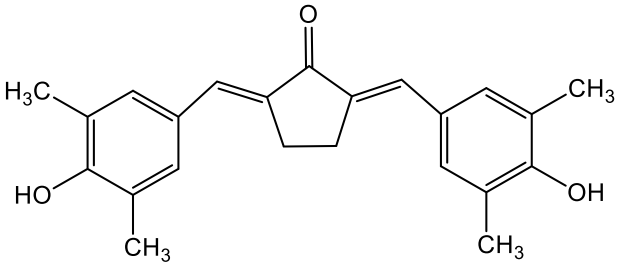


Figure 1. PGV-1

Some researchers have been developed crossed aldol condensation reaction with variety of methods and catalysts. Several methods have been reported, such as, under stirring [2], solvent free reaction [8], and ultrasonic-asisted method [9]. Heterogenous catalysts that usually used for crossed aldol condensation reaction were hydrotalcite [10, 11], ZrO_2-montmorillonit [12] and NaOH/ZrO_2-montmorillonite as cooperative catalyst [13]. While the homogenous catalysts that usually used for aldol condensation were NaOH [2] and H_2SO_4 [14]. Synthesis of vanilinacetone - a benzalacetone derivatives - under stirring for 3 hours provided the yield of 13 - 94% [15]. Solvent-free synthesis of dibenzalacetone's derivative via crossed aldol condensation reaction that conducted by Salehi *et al*. [16] resulted 82-98% yield with reaction time of 2-8 hours. While the synthesis of dibenzalacetone derivatives via ultrasonic-asisted method with a reaction time of about 1.5 hours yielded about 70 to 97% [9]. From the reported researches above, it can be concluded that the synthesis of dibenzalacetone derivatives always resulted higher yields than benzalacetone derivatives synthesis. It because dibenzalacetone resulted from the double aldol condensation on both sides who had Hα, while benzalacetone derivatives should be resulted from mono-condensation on the one hand only. That is why dibenzalacetone is always being a double condensation byproduct of mono-condensation reaction.

Nowadays, trend of synthetic process has been shifting from traditional concept that focused on maximum yield into eco-friendly processes that giving more attention to reaction processes. Eco-friendly reaction process is a reaction which eliminates or reduces waste, save energy and avoid the use of toxic or hazardous compounds [17]. Based on these criterias, several researchers have conducted the synthesis of organic compounds using the Microwave Assisted Organic Synthesis (MAOS) method [4, 9, 10]. The advantage of the synthesis via MAOS reaction are the faster, cleaner, more economic, and environmental friendly. It can also use household microwave ovens and only requires simple glassware and easily being taught to students [20]. MAOS is a new method which is expected in effectively reducing: reaction time, electrical energy use, harmful solvents.

EXPERIMENTAL SECTION

Materials

The materials used for the synthesis include benzaldehyde, 4-methoxybenzaldehyde, 3,4-dimethoxybenzaldehyde cyclohexanone, sodium hydroxide, methanol, chloroform, hexane, aquades and TLC plate of silicagel 60 F254. All the chemicals were purchashed from E-merck.

Instrumentations

Microwave that used for synthesis is SIGMATIC SMO-25SSG 900 W 2450 MHz. Analytical instruments that used for structure elucidation were Nicolet Avatar 360 FTIR for FTIR-spectra investigation and (1H and 13C) Nuclear magnetic resonance (NMR) 400 MHz Agilent together with HMQC. While, the identification analysis were used TLC Scanner (Camag).

Procedure

Optimization of sodium hydroxide concentration to synthesis of (2*E*,6*E*)-2.6-bis(4-methoxybenzylidene)Cyclohexanone (2). Sodium hydroxide (2.5 mmole) in 2 mL methanol was placed in a porcelain crucible. 4-Methoxybenzaldehyde (10 mmole) and cyclohexanone (5 mmole) was consecutively added. Porcelain crucible was covered using aluminum foil and heated in the microwave for 2 minutes with checking every 15 seconds. Reaction products were analyzed using TLC and TLC scanner to determine the yield. The same procedure was repeated using different NaOH concentration of 5; 7.5; 10 and 12.5 mmole. The synthesis efficiency was evaluated from the value of reaction yield based on following calculation:

$$= \frac{\textbf{product weight x purity (area on TLC scanner)}}{\textbf{teorethical weight}}\ \textbf{x 100\%}$$

Synthesis of (2*E*,6*E*)-2.6-dibenzylidenecyclohexanone (1) by MAOS. Sodium hydroxide (5 mmole) was dissolved into 2 mL methanol in a porcelain crucible in which benzaldehyde (10 mmole) and cyclohexanone (5 mmole) was added. The porcelain crucible covered with aluminum foil and then heated in a microwave oven for 2 minutes. The product was dried and weighted to determine the yield of the reaction. The products were then analyzed using TLC, TLC scanner, and identified by FTIR and two dimensional NMR spectrometers. The similar procedure was carried out to synthesis the (2*E*,6*E*)-2.6-bis(4-methoxybenzylidene)cyclohexanone (**2**) and (2*E*,6*E*)-2.6-bis(3,4-dimethoxybenzylidene)cyclohexanone (**3**).

Synthesis of compound (1) with stirring method. Sodium hydroxide (5 mmole) was added to 2 mL of distilled water. Benzaldehyde (10 mmole), cyclohexanone (5 mmole) and 3 mL of ethanol were added to the solution. The mixture was stirred at 10^0C for 120 minutes. Furthermore, the mixture was let stand for 24 hours in the refrigerator until the precipitate was formed. The precipitate was filtered and dried. Further analysis was performed the same as the results of the synthesis using MAOS methods. Structure elucidation had been conducted after the sample was recrystallized from methanol.

FTIR (KBr) (cm^{-1}) of compound **1**: 2926 (C-H stretching), 1604 (C=O), 1573 supported by 1488 (C=C aromatic), 1552 (C=C alkene). 1443 (CH_2 methylene). FTIR (KBr) (cm^{-1}) of compound **2**: 2938 (C-H stretching), 1594 (C=O), 1554 (C=C alkene), 1504 supported by 1416 (C=C aromatic), 1451 (CH_2 methylene), 1162-1112 (C-O), 843 (para subtitution). FTIR (KBr) (cm^{-1}) of compound **3**: 2930 (C-H stretching), 1596 (C=O), 1513 (C=C aromatic), 1451 (CH_2 methylene), 1250-1139 (C-O), 847 (para subtitution) [21].

RESULT AND DISCUSSION

Dibenzylidenecyclohexanone synthesis using MAOS methods produced a dried yellow precipitate, no residual solvents nor alkaline catalyst solution. It is one of the advantages of the MAOS method, which is generating minimal waste. The synthesis resulted compounds **1, 2** and **3** with 98.62; 100 and 93% yields, respectively. While the synthesis under stirring yielded 62.9; 71.09 and 77.9%, respectively (Fig. 5). In this research, just need for 2 minutes to synthesis via MAOS method. The reaction time is shorter than Wang who use 30 minutes and produces 90% in yield [22].

Synthesis of dibenzylidenecyclohexanone mechanism and crossed aldol condensation of benzaldehyde and cyclohexanone were presented on Figure 2-3. Characterization of synthesized compounds **1**, **2** and **3** by using NMR spectrometre are listed in Table 1-3.

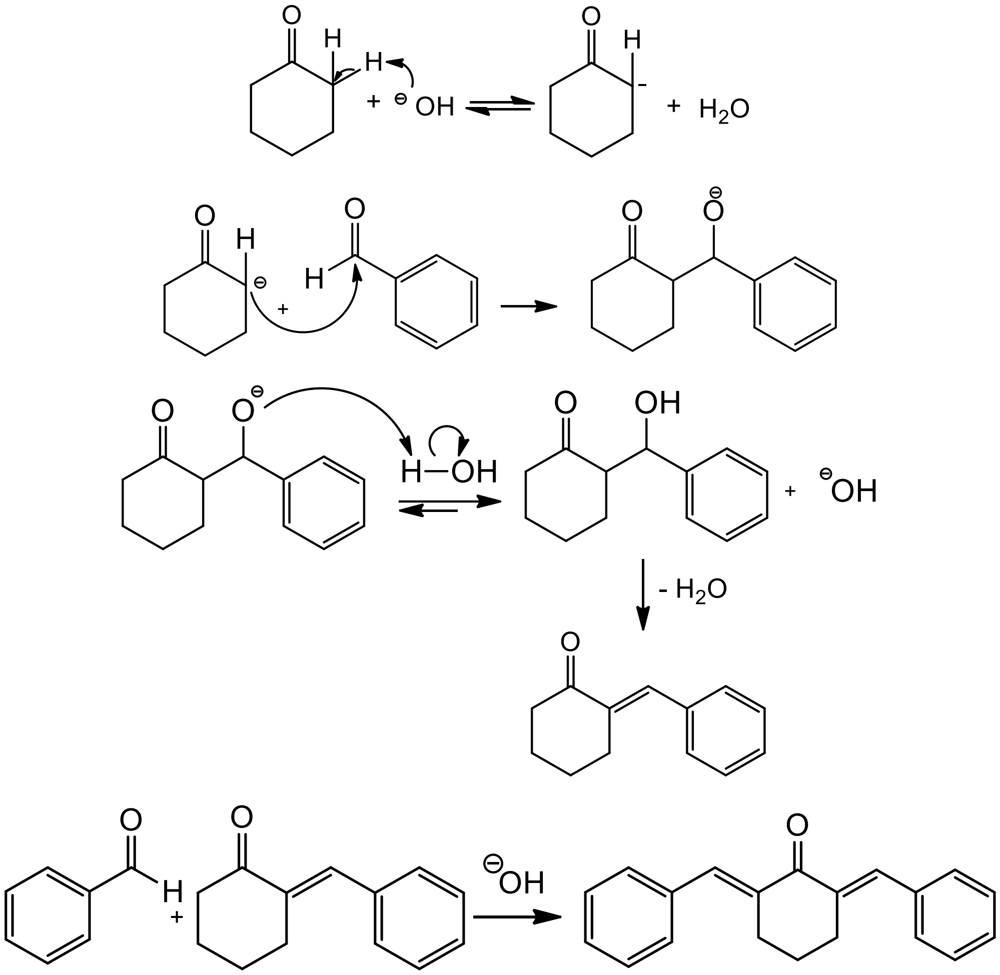
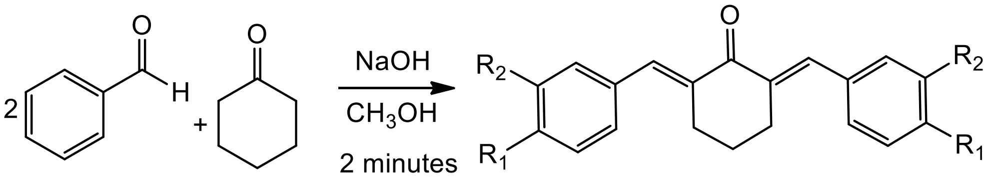


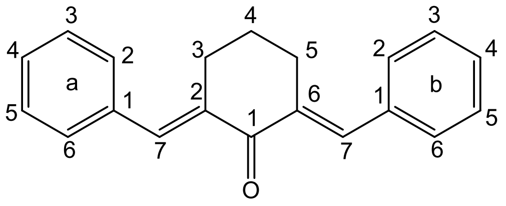
Figure 2. Synthesis of dibenzylidenecyclohexanone mechanism



1 = R_1 = R_2 = H
2 = R_1 = OCH_3, R_2 = H
3 = R_1 = R_2 = OCH_3

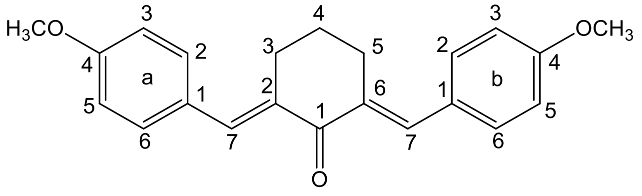
Figure 3. Cross aldol condensation of benzaldehyde derivatives and cyclohexanone

Table 1. NMR (^{1}H and ^{13}C) of compound 1 ($CDCl_3$)



No C	δ (∑H, m, *J* Hz) ppm	δ C (ppm)
1	-	190.3
2,6	-	136.1
3,5	2.9 (4H, m, -)	28.4
4	1.8 (2H, m, -)	23
7	7.8 (2H, s, -)	136.9
1a,1b	-	135.9
2a,6a,2b,6b	7.46 (4H, d, 7.2)	130.3
3a,5a,3b,5b	7.4 (4H, t, 7.2)	128.3
4a,4b	7.3 (2H, d, 7.2)	128.5

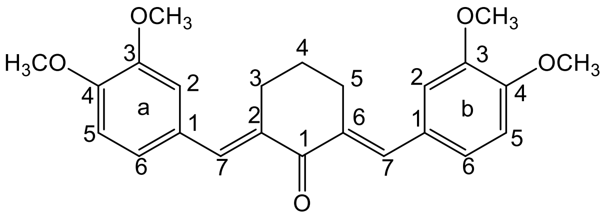
Table 2. NMR (^{1}H and ^{13}C) of compound 2 ($CDCl_3$)



No C	δ (∑H, m, *J* Hz) ppm	δ C (ppm)
1	-	190.2
2,6	-	134.3

3,5	2.9 (4H, t, -)	28.5
4	1.8 (2H, m, -)	23
7	7.7 (2H, s, -)	136
1a,1b	-	128.7
2a,6a,2b,6b	7.45 (4H, d, 7.2)	132.2
3a,5a,3b,5b	6.9 (4H, d, 7.2)	113.8
4a, 4b	-	159.9
4a-OCH_3, 4b-OCH_3	3.8 (6H, s, -)	55.3

Table 3. NMR (^{1}H and ^{13}C) of compound 3 ($CDCl_3$)



No C	δ (∑H, m, *J* Hz) ppm	δ C (ppm)
1	-	190
2,6	-	136
3,5	2.9 (4H, t, -)	28.5
4	1.8 (2H, m, -)	23
7	7.7 (2H, s, -)	134
1a,1b	-	128
2a,2b	7.02 (2H, s, 7.2)	113
3a,3b	-	149
3a-OCH_3, 3b-OCH_3	3.91 (6H, s, -)	55
4a,4b	-	148
4a-OCH_3, 4b-OCH_3	3.92 (6H, s, -)	55
5a, 5b	6.9 (2H, d, 8.3)	110.8
6a, 6b	7.1 (2H, d, 8.3)	123.8

The benzylidenecyclohexanone synthesis begins with the optimization concentration of catalyst. It aims to determine the minimum concentration of catalyst to produce the maximum product. Results of optimization of catalyst concentrations are presented in Figure 4.

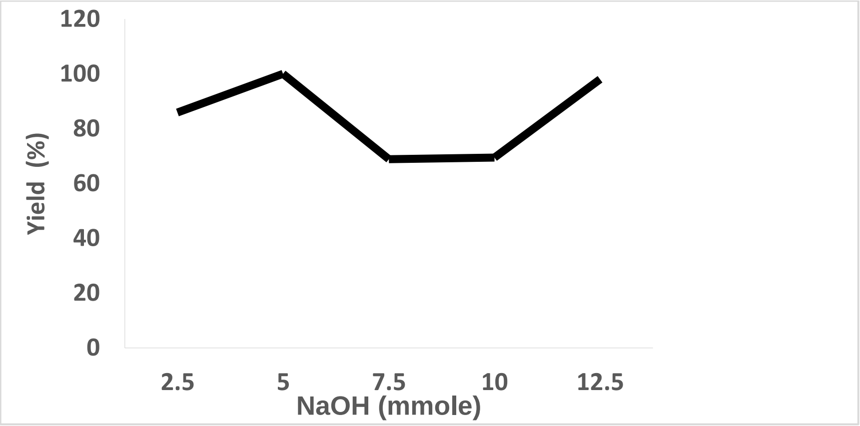


Figure 4. Optimization of NaOH catalyst of compound 2 by MAOS method

Optimum NaOH for the synthesis of compound **2** (5 mmole cyclohexanone, 4-methoxybenzaldehyde 10 mmole) was 5 mmole which produces 100% yield. These results indicated that minimum numbers of moles NaOH have produced maximum products. This is consistent with one of green chemistry pillars, which use minimum chemicals and reduce waste of bases residues.

For the comparison, the stirring method was used to determine the effectiveness of MAOS in the synthesis of dibenzylidenecyclohexanone. Mole numbers of raw materials and catalysts that used were the same. Comparison of the results between MAOS and stirring method was presented in Figure 5.

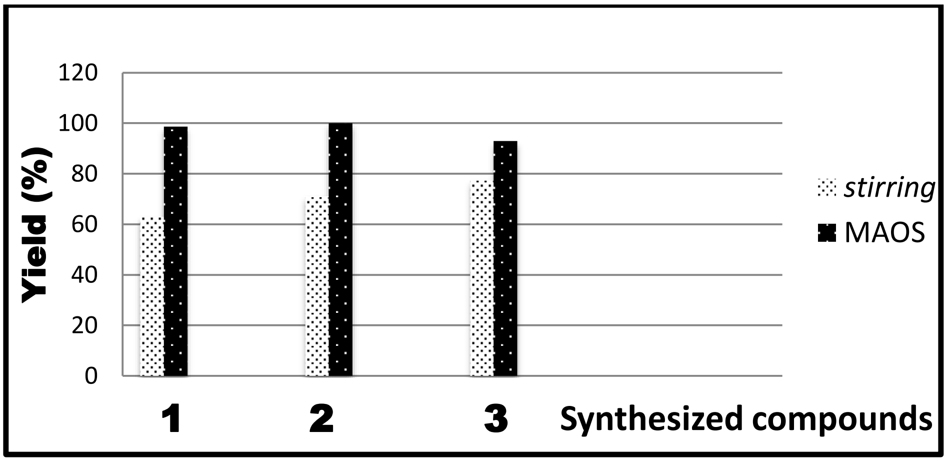


Figure 5. Comparison of the results using MAOS and stirring method

Eco-friendly synthesis process is a chemical reaction using efficient raw material, less waste, free toxic chemicals and a short reaction time [23]. Based on these conditions, synthesis dibenzylidenecyclohexanone was done using MAOS method. MAOS has several advantages compared with conventional heating method. In the conventional method of heating, the reaction container was heated, and the heat was then transfered into the reaction system by convection process. Thus this process took long time and high energy. Heating with microwave is more efficient in terms of energy, homogen temperature and short time. So the main advantages of using the microwave were very short reaction time and high yield [24].

The tools that used in this method is domestic microwave oven. Opinion of some researchers is that domestic microwave oven has a disadvantage in terms of temperature control and low reproducibility. If using a solvent with low boiling point, can lead to over heated reaction. Over pressure can also occur when using a closed reaction system. To avoid over-pressure and over-heated, the crucible porcelain that used was covered by aluminum foil. In this study, solvent that used is methanol because in addition to high enough boiling point, heating using microwave oven require polar solvent. Dielectric polarization dipoles depend on the ability to adjusting the direction of the electric field applied. Seems to make sense to believe that the more polar solvent (with a high dielectric constant) was used, the faster the radiation was absorbed, so that the higher the temperature was obtained [25].

The data in Figure 5 show that the yield of the synthesis using MAOS was larger than that of stirring method. Advantages of MAOS is highly reduce reaction time, increase of yields and product purities to enhance conventionally procces experiments. Very rapid heating at high temperature on MAOS occur based on the implementation of the Arrhenius law. Temperature changes that usually take few hours at reflux temperature, to be perfect in just few minutes using microwave. The rapid heating experienced in microwave-assisted transformations also lead to the changed product distributions compared to a conventional method when the reaction product distribution was controlled by complex temperature-dependent kinetic profiles. This could clarify why microwave-assisted reactions that was performed at an optimized reaction temperature have been established to be cleaner, that guided to less by-products compared to the conventionally method [26].

Crossed aldol condensation reaction is usually performed using a conventional stirring method for a few hours and should left to stand over night. It also required large amount of solvent. Moreover, the results from the conventional method still contained residual catalysts and solvents. Therefore, the use of conventional method requiring high energy for stirring and heating was unwise use of chemicals.

Conclussion

The conclusion from this study is dibenzylidenecyclohexanone and its derivatives can be synthesized by cross aldol condensation using MAOS. Synthesis process using MAOS is better than using stirring method. Based on this research, it can be showed that the product of MAOS synthesis takes very short time reaction, and produced higher yield with almost no waste.

Acknowledgement

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Submission

Authors	Sri Handayani, Cornelia Budimarwanti, Winarto Haryadi
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Microwave-Assisted Organic Reactions: Eco-friendly Synthesis of Dibenzylidenecyclohexanone Derivatives via Crossed Aldol Condensation

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ABSTRAK

The synthesis of dibenzylidenecyclohexanone derivatives *via* environmentally friendly Microwave Assisted Organic Synthesis (MAOS) crossed aldol condensation had been carried out. The condensation reaction to synthesize the dibenzylidenecyclohexanone **8b** was performed by reacting benzaldehyde **4** and cyclohexanone **2** (mole ratio of 2:1) with NaOH as catalyst for 2 minutes under microwace irradiation. The benzaldehyde derivatives used in this study were 4-methoxybenzaldehyde and 3,4-dimethoxybenzaldehyde and gave of (2*E*,6*E*)-bis(4-methoxybenzylidene)cyclohexanone **8a** and (2*E*,6*E*)-bis(3,4-dimethoxybenzylidene)cyclohexanone **8c**, respectively. The study was commenced by searching the optimum concentration of NaOH. The reaction yield was determined by TLC scanner and the structure was elucidated by FTIR and NMR spectrometers. For the comparison, the reaction was also carried out by using stirring method. The results showed that optimum concentration of NaOH was 5 mmole. By using the optimum condition *via* MAOS method, the compounds **8a**, **8b** and **8c** were obtained in 100, 98 and 93%, respectively. The research also showed that synthesis of dibenzylidenecyclohexanones **8** using MAOS was better than stirring method.

Keywords : dibenzylidenecyclohexanone, MAOS, eco-friendly

*Telah dilakukan sintesis dibenzilidensikloheksanon dan turunannya melalui reaksi kondensasi aldol silang yang ramah lingkungan menggunakan metode MAOS. Sintesis dibenzilidensikloheksanon (**8b**) dilakukan melalui reaksi kondensasi antara benzaldehida **4** dan sikloheksanon **2** dalam krus porselen dengan rasio mol 2:1 menggunakan katalis natrium hidroksida selama 2 menit di dalam microwave. Turunan benzaldehida yang digunakan adalah 4-metoksibenzaldehida dan 3,4-dimetoksibenzaldehida untuk mensintesis (2E,6E)-bis(4-metoksibenziliden)sikloheksanon (**8a**) dan (2E,6E)-bis(3,4-dimetoksibenziliden)sikloheksanon (**8c**). Studi dimulai dengan optimasi konsentrasi NaOH sebagai katalis. Rendemen produk ditentukan menggunakan TLC dan TLC scanner dan elusidasi struktur dilakukan menggunakan spectrometer FTIR dan NMR. Sebagai pembanding, dilakukan sintesis senyawa yang sama dengan menggunakan metode pengadukan. Konsentrasi NaOH optimum diperoleh pada 5 mmol. Rendemen hasil sintesis senyawa **8a, 8b**, dan **8c** berturut-turut sebesar 100; 98 dan 93%. Hasil riset membuktikan bahwa hasil* *sintesis dibenzilidensikloheksanon menggunakan metode MAOS lebih baik daripada metode pengadukan.*

Kata kunci : dibenzilidensikloheksanon, MAOS, ramah lingkungan

Introduction.

Benzalacetone has a very interesting structure for being studied and developed. Several benzalacetone analogues have been reported as an active antioxidant [1, 2, 3, 4], antimutagenic [5], and anti-tubercular agent [6]. One of dibenzalacetone derivatives is 2,5-bis(4'-hydroxy-3',5'-dimethyl)-benzylidenecyclopenthanone **1** or is commonly known as the PGV-1 (Fig. 1) was reported for having potential inhibition to the growth of tumors in T47D cells [7]. This compound can be prepared from cyclopentanone and aldehyde *via* crossed aldol condensation. In this study, we would like to synthesize PGV-1 analogue derived from cyclohexanone and benzaldehyde. Due to the similarity of chemical structure, it was expected that the condensation products displayed similar biological activities.

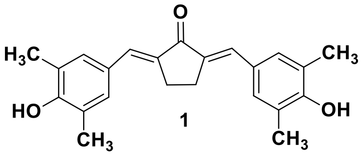

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Figure 1. Structure of PGV-1

Some researchers have been developed crossed aldol condensation reaction with various methods and catalysts. Several methods have been reported, such as, under stirring [2], solvent free reaction [8], and ultrasonic-asisted [9] methods. In addition, heterogenous catalysts has been used for crossed aldol condensation reaction including hydrotalcite [10, 11], ZrO_2-montmorillonit [12] and NaOH/ZrO_2-montmorillonite as cooperative catalyst [13]. While the homogenous catalysts that commonly used for aldol condensation were NaOH [2] and H_2SO_4 [14].

Synthesis of vanilinacetone (a benzalacetone derivatives) *via* crossed aldol condensation under stirring for 3 hours provided the product in 13-94% yields [15]. Solvent-free synthesis of dibenzalacetone's derivatives *via* crossed aldol condensation reaction conducted by Salehi *et al*. [16] resulted 82-98% yield with reaction time of 2-8 hours. While the synthesis of dibenzalacetone derivatives *via* ultrasonic-asisted-method with a reaction time of about 1.5 hours gave the products in 70-97% yield [9].

Nowadays, trend of synthetic process has been shifting from traditional concept that focused on optimum yield into eco-friendly processes that giving more attention to reaction processes. Eco-friendly reaction process is a reaction which eliminates or reduces waste, saves energy and avoids the use of toxic or hazardous compounds [17]. Based on these criteria, several researchers have conducted the synthesis of organic compounds using the Microwave Assisted Organic Synthesis (MAOS) method [4, 9, 10].

The advantageous of the synthesis *via* MAOS reaction are the faster, cleaner, more economic, and environmental friendly than stirring method. It can also use household microwave ovens and only requires simple glassware and more pedagogic [20]. MAOS is a new method which is expected to effectively reduce reaction time, energy and harmful solvents. In connection to our study, we would like to apply MAOS method in the synthesis of dibenzylidenecyclohexanones **8**.

EXPERIMENTAL SECTION

Materials

The materials used for the synthesis of dibenzylidenecyclohexanones **8** included benzaldehyde, 4-methoxybenzaldehyde, 3,4-dimethoxybenzaldehyde, cyclohexanone, sodium hydroxide, methanol, chloroform, *n*-hexane, aquades and TLC plate of silicagel 60 F254. All the chemicals were purchased from E-merck.

Instrumentations

Microwave that used for synthesis was SIGMATIC SMO-25SSG 900 W 2450 MHz. Analytical instruments that used for structure elucidation were Nicolet Avatar 360 FTIR for FTIR-spectra investigation and (^{1}H and ^{13}C) Nuclear magnetic resonance (NMR) 400 MHz Agilent together with HMQC. While, the yield determination and identification analysis were used TLC Scanner (Camag).

Procedure

Optimization of sodium hydroxide concentration on the synthesis of (2*E*,6*E*)-bis(4-methoxybenzylidene)cyclohexanone (8a). Sodium hydroxide (2.5 mmol) in 2 mL methanol was placed in a porcelain crucible. 4-Methoxybenzaldehyde (10 mmol) and cyclohexanone (5 mmol) were consecutively added. Porcelain crucible was covered using aluminum foil and heated in the microwave for 2 minutes. Reaction products were analyzed using TLC and TLC scanner to determine the yield. The same procedure was applied using different NaOH concentrations of 5, 7.5, 10 and 12.5 mmol. The yields were determined by the same method as previous research [13].

Synthesis of (2*E*,6*E*)-dibenzylidenecyclohexanone 8b by MAOS. Sodium hydroxide (5 mmol) was dissolved into 2 mL methanol in a porcelain crucible in which benzaldehyde (10 mmol) and cyclohexanone (5 mmol) were added. The porcelain crucible covered with aluminum foil and then heated in a microwave oven for 2 minutes. The product was dried and weighted to determine the yield of the reaction. The products were then analyzed using TLC, TLC scanner, and identified by FTIR and NMR spectrometers. The similar procedure was carried out to synthesizes the (2*E*,6*E*)-bis(4-methoxybenzylidene)cyclohexanone **8a** and (2*E*,6*E*)-bis(3,4-dimethoxybenzylidene)cyclohexanone **8c**.

Synthesis of (2*E*,6*E*)-dibenzylidenecyclohexanone 8b by stirring method. Sodium hydroxide (5 mmol) was added to 2 mL of distilled water. Benzaldehyde (10 mmole), cyclohexanone (5 mmol) and 3 mL of ethanol were added to the solution. The mixture was stirred at 10°C for 120 minutes. Furthermore, the mixture was allowed to stand for 24 hours in the refrigerator until the precipitate was formed. The precipitate was filtered and dried. Further analysis was performed the same as the results of the synthesis using MAOS methods. Structure elucidation had been conducted after the sample was recrystallized from methanol.

The FTIR (KBr) (cm^{-1}) **8a**: 2938 (C-H stretching), 1594 (C=O), 1554 (C=C alkene), 1504 and 1416 (C=C aromatic), 1451 (CH_2 methylene), 1162-1112 (C-O), 843 (*para* subtitution). FTIR (KBr) (cm^{-1}), **8b**: 2926 (C-H stretching), 1604 (C=O), 1573 and 1488 (C=C aromatic), 1552 (C=C alkene), 1443 (CH_2 methylene). FTIR (KBr) (cm^{-1}) **8c**: 2930 (C-H stretching), 1596 (C=O), 1513 (C=C aromatic), 1451 (CH_2 methylene), 1250-1139 (C-O), 847 (*para* subtitution) [21].

RESULT AND DISCUSSION

Eco-friendly synthesis process is a chemical reaction using efficient raw material, less waste, free toxic chemicals and a short reaction time [23]. Based on these conditions, synthesis dibenzylidenecyclohexanone was done using MAOS method. This method has several advantages compared with conventional heating method. In the conventional method, the reaction container was heated, and the heat was then transfered into the reaction system by convection process. Thus, this process took long time and high energy. Heating with microwave was more efficient in terms of energy, homogen temperature and short time. Therefore, the main advantages of using the microwave were very short reaction time and high yield [24].

The study began with the optimization concentration of NaOH as catalyst. The results showed that MAOS-assisted-synthesis of dibenzylidenecyclohexanone produced a dried yellow precipitate with neither residual solvents nor alkaline catalyst solution. Results of optimization of catalyst concentrations were presented in Figure 2. Optimum amount of NaOH for the synthesis of compound **8a** was 5 mmol which gave the desired product in 100% yield. These results indicated that minimum numbers of moles NaOH which gave maximum products. This is consistent with one of green chemistry principles, which use minimum chemicals and reduce waste of bases residues.

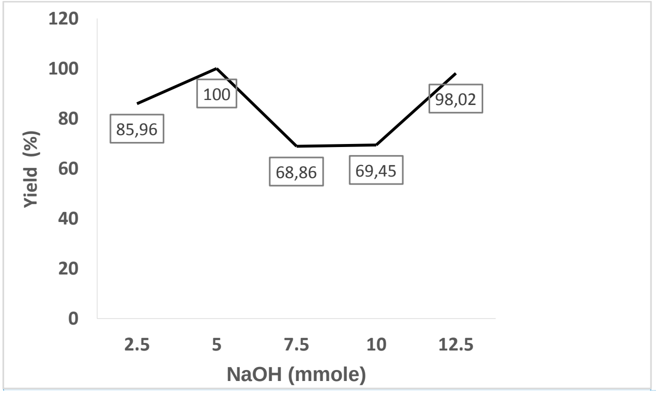

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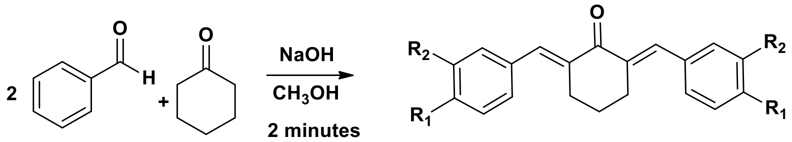
Figure 2. Optimization of NaOH catalyst of compound 8a by MAOS method

With the optimum condition in hand, we employed both benzaldehyde and 3,4-dimethoxybenzaldehyde to give the corresponding dibenzylidenecyclohexanones **8b** and **8c** in 98 and 93% yields, respectively (Fig 3).



8a = R_1 = OCH_3, R_2 = H
8b = R_1 = R_2 = H
8c = R_1 = R_2 = OCH_3

Figure 2. Crossed aldol condensation of cyclohexanone and benzaldehyde derivatives using MAOS method

For the comparison, the stirring method was used to determine the effectiveness of MAOS in the synthesis of dibenzylidenecyclohexanone (Fig. 3). By using stirring method, the yields of dibenzylidenecyclohexanones **8a, 8b** and **8c** were, 71, 63 and 78% yields, respectively. These results indicated that synthesis of dibenzylidenecyclohexanones **8** using MAOS method was more effective than stirring method. In this study, the MAOS method has been proven to be cleaner and produced less by-products compared to the conventional method [26]. In addition, the MAOS reaction time was 2 min, which was shorter than Wang's results which use 30 min and produced the product 90% in yield [22].

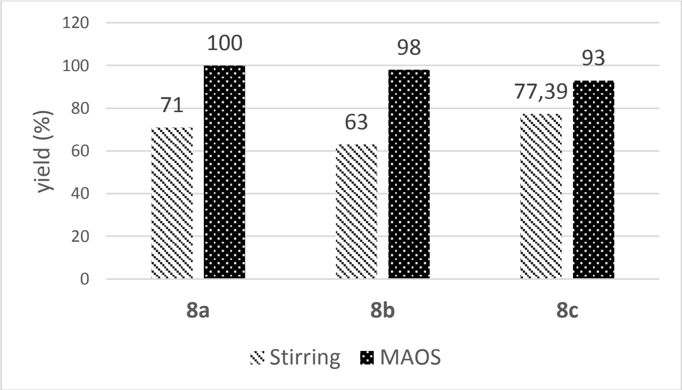


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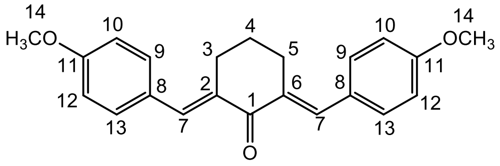
Figure 3. Comparison of the results using MAOS and stirring method

Characterization of synthesized compounds **8a**, **8b** and **8c** by using NMR spectrometer are presented in Table 1-3. HNMR spectra of **8a** shows a multiplet peak at 1.8 ppm and triplet peak at 2.9 ppm of a methylene group. Singlet peak at 7.7 ppm indicate the presence of alkene protons. Methoxy protons appeared at 3.8 ppm, while the aromatic protons appeared as doublet peak at 6.9 and 7:45 ppm. HNMR Spectra **8b** is similar to **8a** but without a singlet peak at 3.8 ppm of methoxy protons. HNMR spectra of **8c** shows a singlet peak at 7.7 ppm indicate the presence of alkene protons. Aromatic protons appeared at 7:02 ppm of singlet peak and two doublet peaks at 6.9 and 7.1 ppm. Methoxy proton indicated by two singlet peaks at 3.91 and 3.92 ppm. Methylene groups appeared at 1.8 and 2.9 ppm as a multiplet and broad triplet peak respectively.

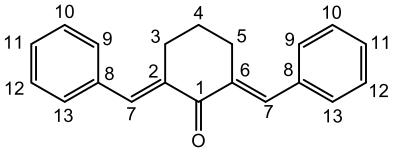
Table 1. NMR (^{1}H and ^{13}C) spectra of compound 8a (CDCl$_3$)



8a

No C	δ (∑H, m, *J* Hz) ppm	δ C (ppm)
1	-	190.2
2,6	-	134.3
3,5	2.92 (4H, t, 5.3)	28.5
4	1.80 (2H, m, -)	23
7	7.76 (2H, s, -)	136
8	-	128.7
9, 13	7.44 (4H, d, 7.2)	132.2
10, 12	6.93 (4H, d, 7.2)	113.8
11	-	159.9
14	3.84 (6H, s, -)	55.3

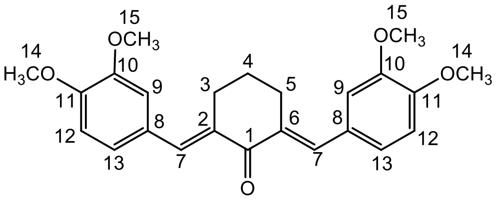
Table 2. NMR (^{1}H and ^{13}C) spectra of compound 8b (CDCl$_3$)



8b

No C	δ (∑H, m, *J* Hz) ppm	δ C (ppm)
1	-	190.3
2,6	-	136.1
3,5	2.93 (4H, m, -)	28.4
4	1.79 (2H, m, -)	23.0
7	7.80 (2H, s, -)	136.9
8	-	135.9
9, 13	7.46 (4H, d, 7.2)	130.3
10, 12	7.42 (4H, t, 7.2)	128.3
11	7.3 (2H, t, 7.2)	128.5

Table 3. NMR (^{1}H and ^{13}C) spectra of compound 8c ($CDCl_3$)



8c

No C	δ (∑H, m, *J* Hz) ppm	δ C (ppm)
1	-	190
2,6	-	136
3,5	2.95 (4H, br t, -)	28.5
4	1.83 (2H, m, -)	23
7	7.75 (2H, s, -)	134
8	-	128
9	7.02 (2H, s, -)	113
10	-	149
11	-	148
12	6.92 (2H, d, 8.3)	110.8
13	7.12 (2H, d, 8.3)	123.8
14	3.92 (6H, s, -)	55
15	3.91 (6H, s, -)	55

The reaction mechanism of crossed aldol condensation of between cyclohexanone and benzaldehyde derivatives was presented on Figure 4. The first step is the formation of a nucleophile **3** by deprotonation of Hα of cyclohexanone by the basic catalyst. Nucleophile addition of enolate **3** to the carbonyl carbon of benzaldehyde, followed with protonation would generate β-hydroxy carbonyl **6**. Benzylidenecyclohexanone **7** was formed *via* dehydration reaction towards **6**. Since there is Hα remained in the intermediate **7**, further crossed aldol condensation reaction might occur to produce dibenzylidenecyclohexanone **8b**.

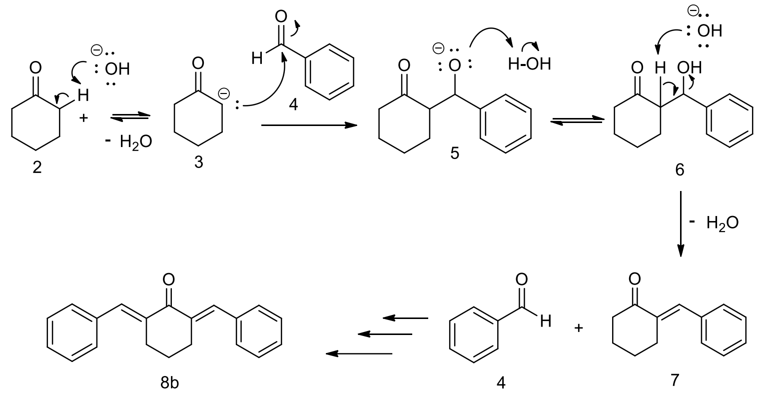


Figure 4. Synthesis of dibenzylidenecyclohexanone mechanism

Crossed aldol condensation reaction is usually performed using a conventional stirring method for a few hours and should left to stand over night. It also required large amount of solvent. To address such limitations, we have performed crossed aldol condensation between cyclohexanone and benzaldehyde derivatives to produce dibenzylidenecyclohexanones *via* MAOS method. In this study, we found that the latter method is more rapid and efficient to provide dibenzylidenecyclohexanones.

Conclusion

In conclusion, three dibenzylidenecyclohexanones have been synthesized *via* crossed aldol condensation using MAOS method. This method has been proven to be more efficient, shorter and cleaner than stirring method.

Acknowledgement

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#25460 Review

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Submission

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Title	Microwave-Assisted Organic Reactions: Eco-friendly Synthesis of Dibenzylidenecyclohexanone Derivatives via Crossed Aldol Condensation
Section	Note
Editor	Tutik Wahyuningsih ✉ Dwi Siswanta ✉

Peer Review

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NOTE

Microwave-Assisted Organic Reactions: Eco-friendly Synthesis of Dibenzylidenecyclohexanone Derivatives via Crossed Aldol Condensation

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ABSTRACT

The synthesis of dibenzylidenecyclohexanone derivatives via environmentally friendly Microwave Assisted Organic Synthesis (MAOS) crossed aldol condensation had been carried out. The condensation reaction to synthesize the dibenzylidenecyclohexanone ***8b*** *was performed by reacting benzaldehyde* ***4*** *and cyclohexanone* ***2*** *(mole ratio of 2:1) with NaOH as catalyst for 2 min under microwave irradiation. The benzaldehyde derivatives used in this study were 4-methoxybenzaldehyde and 3,4-dimethoxybenzaldehyde and gave of (2E,6E)-bis(4-methoxy benzylidene)cyclohexanone* ***8a*** *and (2E,6E)-bis(3,4-dimethoxybenzylidene)cyclohexanone* ***8c****, respectively. The study was commenced by searching the optimum concentration of NaOH. The reaction yield was determined by TLC scanner and the structure was elucidated by FTIR and NMR spectrometers. For the comparison, the reaction was also carried out by using stirring method. The results showed that optimum concentration of NaOH was 5 mmole. By using the optimum condition via MAOS method, the compounds* ***8a****,* ***8b*** *and* ***8c*** *were obtained in 100, 98 and 93%, respectively. The research also showed that synthesis of dibenzylidenecyclohexanones* ***8*** *using MAOS was better than stirring method.*

Keywords: *dibenzylidenecyclohexanone; MAOS; eco-friendly*

ABSTRAK

*Telah dilakukan sintesis dibenzilidensikloheksanon dan turunannya melalui reaksi kondensasi aldol silang yang ramah lingkungan menggunakan metode MAOS. Sintesis dibenzilidensikloheksanon (****8b****) dilakukan melalui reaksi kondensasi antara benzaldehida* ***4*** *dan sikloheksanon* ***2*** *dalam krus porselen dengan rasio mol 2:1 menggunakan katalis natrium hidroksida selama 2 menit di dalam microwave. Turunan benzaldehida yang digunakan adalah 4-metoksibenzaldehida dan 3,4-dimetoksibenzaldehida untuk mensintesis (2E,6E)-bis(4-metoksibenziliden) siklo heksanon (****8a****) dan (2E,6E)-bis(3,4-dimetoksibenziliden)sikloheksanon (****8c****). Studi dimulai dengan optimasi konsentrasi NaOH sebagai katalis. Rendemen produk ditentukan menggunakan TLC dan TLC scanner dan elusidasi struktur dilakukan menggunakan spectrometer FTIR dan NMR. Sebagai pembanding, dilakukan sintesis senyawa yang sama dengan menggunakan metode pengadukan. Konsentrasi NaOH optimum diperoleh pada 5 mmol. Rendemen hasil sintesis senyawa* ***8a****,* ***8b****, dan* ***8c*** *berturut-turut sebesar 100, 98 dan 93%. Hasil riset membuktikan bahwa hasil sintesis dibenzilidensikloheksanon menggunakan metode MAOS lebih baik daripada metode pengadukan.*

Kata Kunci: *dibenzilidensikloheksanon; MAOS; ramah lingkungan*

INTRODUCTION

Benzalacetone has a very interesting structure for being studied and developed. Several benzalacetone analogues have been reported as an active antioxidant [1-4], antimutagenic [5], and anti-tubercular agent [6]. One of dibenzalacetone derivatives is 2,5-bis(4'-hydroxy-3',5'-dimethyl)-benzylidenecyclopenthanone **1** or is commonly known as the PGV-1 (Fig. 1) was reported for having potential inhibition to the growth of tumors in T47D cells [7]. This compound can be prepared from cyclopentanone and aldehyde *via* crossed aldol condensation. In this study, we would like to synthesize PGV-1 analogue derived from cyclohexanone and benzaldehyde. Due to the similarity of chemical structure, it was expected that the condensation

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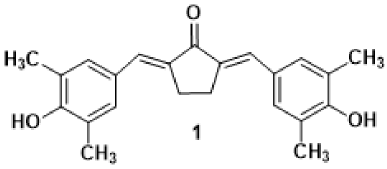


Fig 1. Structure of PGV-1

products displayed similar biological activities.

Some researchers have been developed crossed aldol condensation reaction with various methods and catalysts. Several methods have been reported, such as, under stirring [2], solvent free reaction [8], and ultrasonic-assisted [9] methods. In addition, heterogeneous catalysts has been used for crossed aldol condensation reaction including hydrotalcite [10-11], ZrO_2-montmorillonit [12] and NaOH/ZrO_2-montmorillonite as cooperative catalyst [13]. While the homogenous catalysts that commonly used for aldol condensation were NaOH [2] and H_2SO_4 [14].

Synthesis of vanillinacetone (a benzalacetone derivatives) *via* crossed aldol condensation under stirring for 3 h yielded the product in 13-94% yields [15]. Solvent-free synthesis of dibenzalacetone's derivatives *via* crossed aldol condensation reaction conducted by Salehi et al. [16] resulted in 82-98% yield with reaction time of 2-8 h. While the synthesis of dibenzalacetone derivatives *via* ultrasonic-assisted-method with a reaction time of about 1.5 h gave the products in 70-97% yield [9].

Nowadays, trend of synthetic process has been shifting from traditional concept that focused on optimum yield into eco-friendly processes that giving more attention to reaction processes. Eco-friendly reaction process is a reaction which eliminates or reduces waste, saves energy and avoids the use of toxic or hazardous compounds [17]. Based on these criteria, several researchers have conducted the synthesis of organic compounds using the Microwave Assisted Organic Synthesis (MAOS) method [4,9-10]. The advantageous of the synthesis *via* MAOS reaction are the faster, cleaner, more economic, and environmental friendly than stirring method. It can also use household microwave ovens and only requires simple glassware and more pedagogic [20]. MAOS is a new method which is expected to effectively reduce reaction time, energy and harmful solvents. In connection to our study, we would like to apply MAOS method in the synthesis of dibenzylidenecyclohexanones **8**.

EXPERIMENTAL SECTION

Materials

The materials used for the synthesis of dibenzylidenecyclohexanones **8** included benzaldehyde, 4-methoxybenzaldehyde, 3,4-dimethoxybenzaldehyde, cyclohexanone, sodium hydroxide, methanol, chloroform, *n*-hexane and TLC plate of silica gel 60 F254. All the chemicals were purchased from E-Merck.

Instrumentation

Microwave that used for synthesis was SIGMATIC SMO-25SSG 900 W 2450 MHz. Analytical instruments that used for structure elucidation were Nicolet Avatar 360 FTIR for FTIR-spectra investigation and (^{1}H and ^{13}C) Nuclear magnetic resonance (NMR) 400 MHz Agilent together with HMQC. While, the yield determination and identification analysis were used TLC Scanner (Camag).

Procedure

Optimization of sodium hydroxide concentration on the synthesis of (2E,6E)-bis(4-methoxybenzylidene) cyclohexanone (8a)

Sodium hydroxide (2.5 mmol) in 2 mL methanol was placed in a porcelain crucible. 4-methoxy benzaldehyde (10 mmol) and cyclohexanone (5 mmol) were consecutively added. Porcelain crucible was covered using aluminum foil and heated in the microwave for 2 min. Reaction products were analyzed using TLC and TLC scanner to determine the yield. The same procedure was applied using different NaOH concentrations of 5, 7.5, 10 and 12.5 mmol. The yields were determined by the same method as previous research [13].

Synthesis of (2E,6E)-dibenzylidenecyclohexanone 8b by MAOS

Sodium hydroxide (5 mmol) was dissolved into 2 mL methanol in a porcelain crucible in which benzaldehyde (10 mmol) and cyclohexanone (5 mmol) were added. The porcelain crucible covered with aluminum foil and then heated in a microwave oven for 2 min. The product was dried and weighted to determine the yield of the reaction. The products were then analyzed using TLC, TLC scanner, and identified by FTIR and NMR spectrometers. The similar procedure was carried out to synthesizes the (2*E*,6*E*)-bis(4-methoxybenzylidene)cyclohexanone **8a** and (2*E*, 6*E*)-bis(3,4-dimethoxybenzylidene)cyclohexanone **8c**.

Synthesis of (2E,6E)-dibenzylidenecyclohexanone 8b by stirring method

Sodium hydroxide (5 mmol) was added to 2 mL of distilled water. Benzaldehyde (10 mmole), cyclohexanone (5 mmol) and 3 mL of ethanol were added to the solution. The mixture was stirred at 10 °C for 120 min. Furthermore, the mixture was allowed to stand for 24 h in the refrigerator until the precipitate was formed. The precipitate was filtered off, dried analysis using same method as for MAOS products. Further analysis was performed by similar with the results of the synthesis using MAOS methods. Structure elucidation had been conducted after the sample was recrystallized from methanol.

The FTIR (KBr) (cm^{-1}) **8a**: 2938 (C-H stretching), 1594 (C=O), 1554 (C=C alkene), 1504 and 1416 (C=C aromatic), 1451 (CH_2 methylene), 1162-1112 (C-O), 843 (*para* substitution). FTIR (KBr) (cm^{-1}), **8b**: 2926 (C-H stretching), 1604 (C=O), 1573 and 1488 (C=C aromatic), 1552 (C=C alkene), 1443 (CH_2 methylene). FTIR (KBr) (cm^{-1}) **8c**: 2930 (C-H stretching), 1596 (C=O), 1513 (C=C aromatic), 1451 (CH_2 methylene), 1250-1139 (C-O), 847 (*para* substitution) [21].

RESULT AND DISCUSSION

Eco-friendly synthesis process is a chemical reaction using efficient raw material, less waste, free toxic chemicals and a short reaction time [23]. Based on these conditions, synthesis dibenzylidenecyclohexanone was done using MAOS method. This method has several advantages compared with conventional heating method. In the conventional method, the reaction container was heated, and the heat was then transfered into the reaction system by convection process. Thus, this process took long time and high energy. Heating with microwave was more efficient in terms of energy, homogen temperature and short time. Therefore, the main advantages of using the microwave were very short reaction time and high yield [24].

The study began with the optimization concentration of NaOH as catalyst. The results showed that MAOS-assisted-synthesis of dibenzylidenecyclo hexanone produced a dried yellow precipitate with neither residual solvents nor alkaline catalyst solution. Results of optimization of catalyst concentrations were presented in Fig. 2. Optimum amount of NaOH for the synthesis of compound **8a** was 5 mmol which gave the desired product in 100% yield. These results indicated that minimum numbers of moles NaOH which gave maximum products. This is consistent with one of green chemistry principles, which use minimum chemicals and reduce waste of bases residues.

With the optimum condition in hand, we employed both benzaldehyde and 3,4-dimethoxybenzaldehyde to give the corresponding dibenzylidenecyclohexanones **8b** and **8c** in 98 and 93% yields, respectively (Fig. 3).

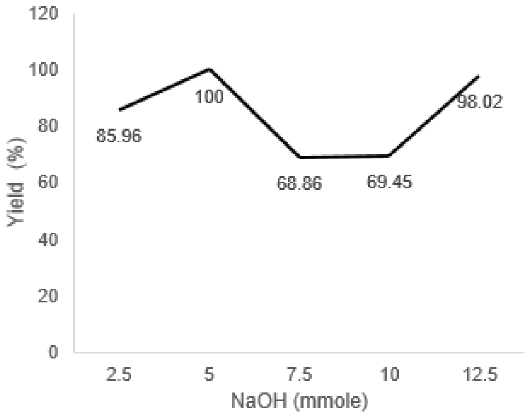


Fig 2. Optimization of NaOH catalyst of compound **8a** by MAOS method

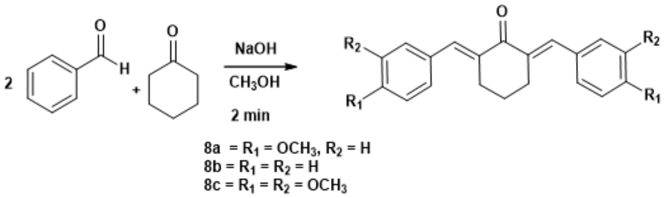


Fig 3. Crossed aldol condensation of cyclohexanone and benzaldehyde derivatives using MAOS method

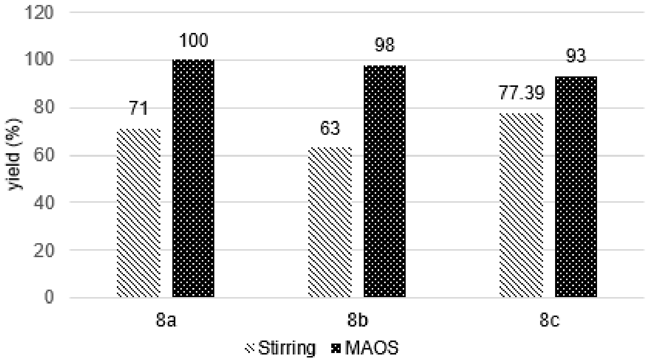


Fig 4. Comparison of the results using MAOS and stirring method

For the comparison, the stirring method was carried out to determine the effectiveness of MAOS in the synthesis of dibenzylidenecyclohexanone (Fig. 4). By using stirring method, the yields of dibenzylidenecyclohexanones **8a**, **8b** and **8c** were, 71, 63 and 78% yields, respectively. These results indicated that synthesis of dibenzylidenecyclo hexanones **8** using MAOS method was more effective than stirring method. In this study, the MAOS method has been proven to be cleaner and produced less by-products compared to the conventional method [26]. In addition, the MAOS reaction time was 2 min, which was shorter than Wang's results which use 30 min and produced the product in 90% yield [22].

Characterization of synthesized compounds **8a**, **8b** and **8c** by using NMR spectrometer are presented in Table 1-3. HNMR spectra of **8a** shows a multiplet peak at 1.8 ppm and triplet peak at 2.9 ppm of a methylene group. Singlet peak at 7.7 ppm indicate the

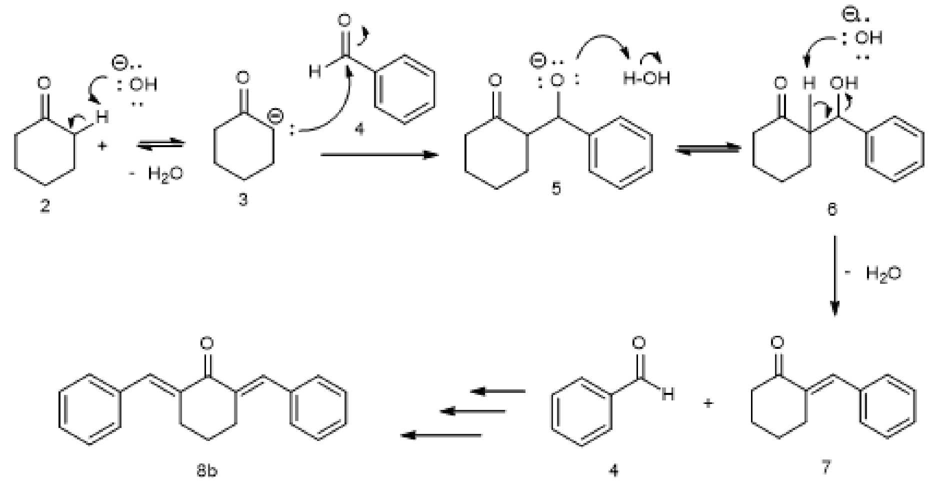
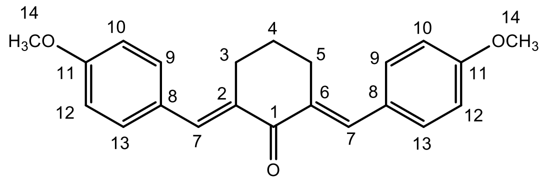


Fig 5. Synthesis of dibenzylidenecyclohexanone mechanism

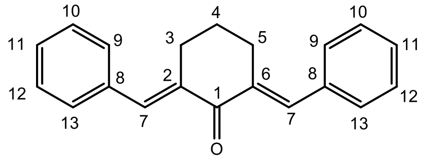
Table 1. NMR (^{1}H and ^{13}C) spectra of compound 8a (CDCl$_3$)



8a

No C	δ (∑H, m, *J* Hz) ppm	δ C (ppm)
1	-	190.2
2, 6	-	134.3
3, 5	2.92 (4H, t, 5.3)	28.5
4	1.80 (2H, m, -)	23.0
7	7.76 (2H, s, -)	136.0
8	-	128.7
9, 13	7.44 (4H, d, 7.2)	132.2
10, 12	6.93 (4H, d, 7.2)	113.8
11	-	159.9
14	3.84 (6H, s, -)	55.3

Table 2. NMR (^{1}H and ^{13}C) spectra of compound **8b** (CDCl$_3$)



8b

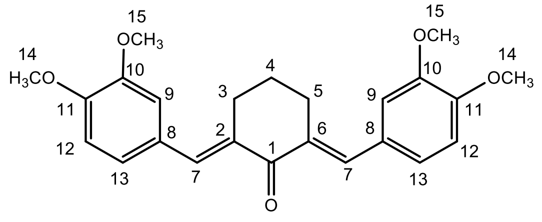
No C	δ (∑H, m, *J* Hz) ppm	δ C (ppm)
1	-	190.3
2 ,6	-	136.1
3, 5	2.93 (4H, m, -)	28.4
4	1.79 (2H, m, -)	23.0
7	7.80 (2H, s, -)	136.9
8	-	135.9
9, 13	7.46 (4H, d, 7.2)	130.3
10, 12	7.42 (4H, t, 7.2)	128.3
11	7.30 (2H, t, 7.2)	128.5

presence of alkene protons. Methoxy protons appeared at 3.8 ppm, while the aromatic protons appeared as doublet peak at 6.9 and 7:45 ppm. HNMR Spectra **8b** is similar to **8a** but without a singlet peak at 3.8 ppm of methoxy protons. HNMR spectra of **8c** shows a singlet peak at 7.7 ppm indicate the presence of alkene protons. Aromatic protons appeared at 7:02 ppm of singlet peak and two doublet peaks at 6.9 and 7.1 ppm. Methoxy proton indicated by two singlet peaks at 3.91 and 3.92 ppm. Methylene groups appeared at 1.8 and 2.9 ppm as a multiplet and broad triplet peak respectively.

The reaction mechanism of crossed aldol condensation of between cyclohexanone and benzaldehyde derivatives was presented on Fig. 5. The first step is the formation of a nucleophile **3** by deprotonation of Hα of cyclohexanone by the basic catalyst. Nucleophile addition of enolate **3** to the carbonyl carbon of benzaldehyde, followed with protonation would generate β-hydroxy carbonyl **6**. Benzylidenecyclohexanone **7** was formed *via* dehydration reaction towards **6**. Since there is Hα remained in the intermediate **7**, further crossed aldol condensation reaction might occur to produce dibenzylidenecyclohexanone **8b**.

Crossed aldol condensation reaction is usually performed using a conventional stirring method for a few hours and should left to stand over night. It also required large amount of solvent. To address such limitations, we have performed crossed aldol condensation between cyclohexanone and benzaldehyde derivatives to produce dibenzylidene cyclohexanones *via* MAOS method. In this study, we found that the latter method is more rapid and efficient to provide dibenzylidenecyclohexanones.

Table 3. NMR (^{1}H and ^{13}C) spectra of compound **8c** ($CDCl_3$)



8c

No C	δ (∑H, m, *J* Hz) ppm	δ C (ppm)
1	-	190.0
2, 6	-	136.0
3, 5	2.95 (4H, br t, -)	28.5
4	1.83 (2H, m, -)	23.0
7	7.75 (2H, s, -)	134.0
8	-	128.0
9	7.02 (2H, s, -)	113.0
10	-	149.0
11	-	148.0
12	6.92 (2H, d, 8.3)	110.8
13	7.12 (2H, d, 8.3)	123.8
14	3.92 (6H, s, -)	55.0
15	3.91 (6H, s, -)	55.0

CONCLUSION

In conclusion, three dibenzylidenecyclohexanones have been synthesized *via* crossed aldol condensation using MAOS method. This method has been proven to be more efficient, shorter and cleaner than stirring method.

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NOTE

Microwave-Assisted Organic Reactions: Eco-friendly Synthesis of Dibenzylidenecyclohexanone Derivatives via Crossed Aldol Condensation

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ABSTRACT

The synthesis of dibenzylidenecyclohexanone derivatives via environmentally friendly Microwave Assisted Organic Synthesis (MAOS) crossed aldol condensation had been carried out. The condensation reaction to synthesize the dibenzylidenecyclohexanone ***8b*** *was performed by reacting benzaldehyde* ***4*** *and cyclohexanone* ***2*** *(mole ratio of 2:1) with NaOH as catalyst for 2 min under microwave irradiation. The benzaldehyde derivatives used in this study were 4-methoxybenzaldehyde and 3,4-dimethoxybenzaldehyde and gave of (2E,6E)-bis(4-methoxy benzylidene)cyclohexanone* ***8a*** *and (2E,6E)-bis(3,4-dimethoxybenzylidene)cyclohexanone* ***8c****, respectively. The study was commenced by searching the optimum concentration of NaOH. The reaction yield was determined by TLC scanner and the structure was elucidated by FTIR and NMR spectrometers. For the comparison, the reaction was also carried out by using stirring method. The results showed that optimum concentration of NaOH was 5 mmole. By using the optimum condition via MAOS method, the compounds* ***8a****,* ***8b*** *and* ***8c*** *were obtained in 100, 98 and 93%, respectively. The research also proved that the method of dibenzylidenecyclohexanones (****8****) synthesis using MAOS was more efficient than stirring method.*

Keywords: *dibenzylidenecyclohexanone; MAOS; eco-friendly*

ABSTRAK

*Telah dilakukan sintesis dibenzilidensikloheksanon dan turunannya melalui reaksi kondensasi aldol silang yang ramah lingkungan menggunakan metode MAOS. Sintesis dibenzilidensikloheksanon (****8b****) dilakukan melalui reaksi kondensasi antara benzaldehida* ***4*** *dan sikloheksanon* ***2*** *dalam krus porselen dengan rasio mol 2:1 menggunakan katalis natrium hidroksida selama 2 menit di dalam microwave. Turunan benzaldehida yang digunakan adalah 4-metoksibenzaldehida dan 3,4-dimetoksibenzaldehida untuk mensintesis (2E,6E)-bis(4-metoksibenziliden) siklo heksanon (****8a****) dan (2E,6E)-bis(3,4-dimetoksibenziliden)sikloheksanon (****8c****). Studi dimulai dengan optimasi konsentrasi NaOH sebagai katalis. Rendemen produk ditentukan menggunakan TLC dan TLC scanner dan elusidasi struktur dilakukan menggunakan spectrometer FTIR dan NMR. Sebagai pembanding, dilakukan sintesis senyawa yang sama dengan menggunakan metode pengadukan. Konsentrasi NaOH optimum diperoleh pada 5 mmol. Rendemen hasil sintesis senyawa* ***8a****,* ***8b****, dan* ***8c*** *berturut-turut sebesar 100, 98 dan 93%. Hasil riset membuktikan bahwa metode sintesis dibenzilidensikloheksanon menggunakan MAOS lebih efisien daripada metode pengadukan.*

Kata Kunci: *dibenzilidensikloheksanon; MAOS; ramah lingkungan*

INTRODUCTION

Benzalacetone has a very interesting structure for being studied and developed. Several benzalacetone analogues have been reported as an active antioxidant [1-4], antimutagenic [5], and anti-tubercular agent [6]. One of dibenzalacetone derivatives is 2,5-bis(4'-hydroxy-3',5'-dimethyl)-benzylidenecyclopenthanone **1** or is commonly known as the PGV-1 (Fig. 1) was reported for having potential inhibition to the growth of tumors in T47D cells [7]. This compound can be prepared from cyclopentanone and aldehyde *via* crossed aldol condensation. In this study, we would like to synthesize PGV-1 analogue derived from cyclohexanone and benzaldehyde. Due to the similarity of chemical structure, it was expected that the condensation products displayed similar biological activities.

Some researchers have been developed crossed

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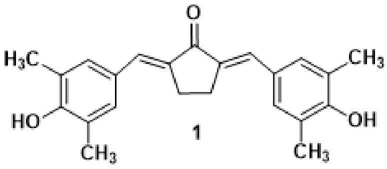


Fig 1. Structure of PGV-1

aldol condensation reaction with various methods and catalysts. Several methods have been reported, such as, under stirring [2], solvent free reaction [8], and ultrasonic-assisted [9] methods. In addition, heterogeneous catalysts has been used for crossed aldol condensation reaction including hydrotalcite [10-11], ZrO_2-montmorillonit [12] and NaOH/ZrO_2-montmorillonite as cooperative catalyst [13]. While the homogenous catalysts that commonly used for aldol condensation were NaOH [2] and H_2SO_4 [14].

Synthesis of vanillinacetone (a benzalacetone derivatives) *via* crossed aldol condensation under stirring for 3 h yielded the product in 13-94% yields [15]. Solvent-free synthesis of dibenzalacetone's derivatives *via* crossed aldol condensation reaction conducted by Salehi et al. [16] resulted in 82-98% yield with reaction time of 2-8 h. While the synthesis of dibenzalacetone derivatives *via* ultrasonic-assisted-method with a reaction time of about 1.5 h gave the products in 70-97% yield [9].

Nowadays, trend of synthetic process has been shifting from traditional concept that focused on optimum yield into eco-friendly processes that giving more attention to reaction processes. Eco-friendly reaction process is a reaction which eliminates or reduces waste, saves energy and avoids the use of toxic or hazardous compounds [17]. Based on these criteria, several researchers have conducted the synthesis of organic compounds using the Microwave Assisted Organic Synthesis (MAOS) method [4,9-10]. The advantageous of the synthesis *via* MAOS reaction are the faster, cleaner, more economic, and environmental friendly than stirring method. It can also use household microwave ovens and only requires simple glassware and more pedagogic [20]. MAOS is a new method which is expected to effectively reduce reaction time, energy and harmful solvents. In connection to our study, we would like to apply MAOS method in the synthesis of dibenzylidenecyclohexanones **8**.

EXPERIMENTAL SECTION

Materials

The materials used for the synthesis of dibenzylidenecyclohexanones **8** included benzaldehyde, 4-methoxybenzaldehyde, 3,4-dimethoxybenzaldehyde, cyclohexanone, sodium hydroxide, methanol, chloroform, *n*-hexane and TLC plate of silica gel 60 F254. All the chemicals were purchased from E-Merck.

Instrumentation

Microwave that used for synthesis was SIGMATIC SMO-25SSG 900 W 2450 MHz. Analytical instruments that used for structure elucidation were Nicolet Avatar 360 FTIR for FTIR-spectra investigation and (^{1}H and ^{13}C) Nuclear magnetic resonance (NMR) 400 MHz Agilent together with HMQC. While, the yield determination and identification analysis were used TLC Scanner (Camag).

Procedure

Optimization of sodium hydroxide concentration on the synthesis of (2E,6E)-bis(4-methoxybenzylidene) cyclohexanone (8a)

Sodium hydroxide (2.5 mmol) in 2 mL methanol was placed in a porcelain crucible. 4-methoxy benzaldehyde (10 mmol) and cyclohexanone (5 mmol) were consecutively added. Porcelain crucible was covered using aluminum foil and heated in the microwave for 2 min. Reaction products were analyzed using TLC and TLC scanner to determine the yield. The same procedure was applied using different NaOH concentrations of 5, 7.5, 10 and 12.5 mmol. The yields were determined by the same method as previous research [13].

Synthesis of (2E,6E)-dibenzylidenecyclohexanone 8b by MAOS

Sodium hydroxide (5 mmol) was dissolved into 2 mL methanol in a porcelain crucible in which benzaldehyde (10 mmol) and cyclohexanone (5 mmol) were added. The porcelain crucible covered with aluminum foil and then heated in a microwave oven for 2 min. The product was dried and weighted to determine the yield of the reaction. The products were then analyzed using TLC, TLC scanner, and identified by FTIR and NMR spectrometers. The similar procedure was carried out to synthesizes the (2*E*,6*E*)-bis(4-methoxybenzylidene)cyclohexanone **8a** and (2*E*, 6*E*)-bis(3,4-dimethoxybenzylidene)cyclohexanone **8c**.

Synthesis of (2E,6E)-dibenzylidenecyclohexanone 8b by stirring method

Sodium hydroxide (5 mmol) was added to 2 mL of distilled water. Benzaldehyde (10 mmole), cyclohexanone (5 mmol) and 3 mL of ethanol were added to the solution. The mixture was stirred at 10 °C for 120 min. Furthermore, the mixture was allowed to stand for 24 h in the refrigerator until the precipitate was formed. The precipitate was filtered off, dried analysis using same method as for MAOS products. Further analysis was performed by similar with the results of the synthesis using MAOS methods. Structure elucidation had been conducted after the sample was recrystallized from methanol.

The FTIR (KBr) (cm^{-1}) **8a**: 2938 (C-H stretching), 1594 (C=O), 1554 (C=C alkene), 1504 and 1416 (C=C aromatic), 1451 (CH_2 methylene), 1162-1112 (C-O), 843 (*para* substitution). FTIR (KBr) (cm^{-1}), **8b**: 2926 (C-H stretching), 1604 (C=O), 1573 and 1488 (C=C aromatic), 1552 (C=C alkene), 1443 (CH_2 methylene). FTIR (KBr) (cm^{-1}) **8c**: 2930 (C-H stretching), 1596 (C=O), 1513 (C=C aromatic), 1451 (CH_2 methylene), 1250-1139 (C-O), 847 (*para* substitution) [21].

RESULT AND DISCUSSION

Eco-friendly synthesis process is a chemical reaction using efficient raw material, less waste, free toxic chemicals and a short reaction time [23]. Based on these conditions, synthesis dibenzylidenecyclohexanone was done using MAOS method. This method has several advantages compared with conventional heating method. In the conventional method, the reaction container was heated, and the heat was then transfered into the reaction system by convection process. Thus, this process took long time and high energy. Heating with microwave was more efficient in terms of energy, homogen temperature and short time. Therefore, the main advantages of using the microwave were very short reaction time and high yield [24].

The study began with the optimization concentration of NaOH as catalyst. The results showed that MAOS-assisted-synthesis of dibenzylidenecyclo hexanone produced a dried yellow precipitate with neither residual solvents nor alkaline catalyst solution. Results of optimization of catalyst concentrations were presented in Fig. 2. Optimum amount of NaOH for the synthesis of compound **8a** was 5 mmol which gave the desired product in 100% yield. These results indicated that minimum numbers of moles NaOH which gave maximum products. This is consistent with one of green chemistry principles, which use minimum chemicals and reduce waste of bases residues.

With the optimum condition in hand, we employed both benzaldehyde and 3,4-dimethoxybenzaldehyde to give the corresponding dibenzylidenecyclohexanones **8b** and **8c** in 98 and 93% yields, respectively (Fig. 3).

For the comparison, the stirring method was carried out to determine the effectiveness of MAOS in the synthesis of dibenzylidenecyclohexanone (Fig. 4). By using stirring method, the yields of dibenzylidenecyclohexanones **8a**, **8b** and **8c** were, 71, 63 and 78% yields, respectively. These results indicated that synthesis of dibenzylidenecyclohexanones **8** using MAOS method was more effective than stirring method. In this study, the MAOS method has been proven to be cleaner and produced less by-products compared to the conventional method [26]. In addition, the MAOS reaction time was 2 min, which was shorter than Wang's results which use 30 min and produced the product in 90% yield [22].

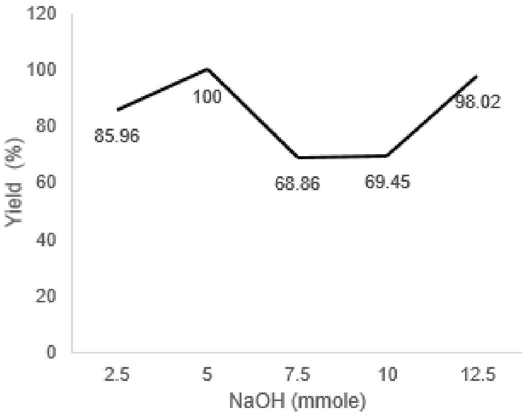


Fig 2. Optimization of NaOH catalyst of compound **8a** by MAOS method

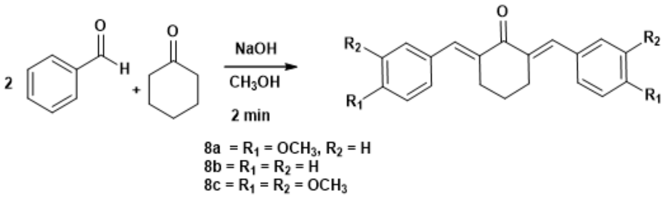


Fig 3. Crossed aldol condensation of cyclohexanone and benzaldehyde derivatives using MAOS method

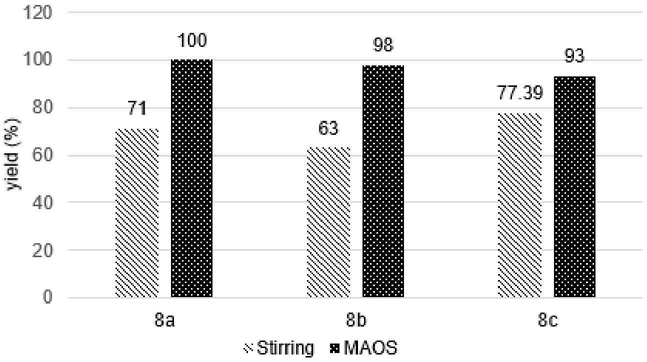


Fig 4. Comparison of the results using MAOS and stirring method

Characterization of synthesized compounds **8a**, **8b** and **8c** by using NMR spectrometer are presented in Table 1-3. HNMR spectra of **8a** shows a multiplet peak at 1.8 ppm and triplet peak at 2.9 ppm of a methylene group. Singlet peak at 7.7 ppm indicate the presence of alkene protons. Methoxy protons appeared at 3.8 ppm, while the aromatic protons appeared as doublet peak at 6.9 and 7:45 ppm. HNMR Spectra **8b**

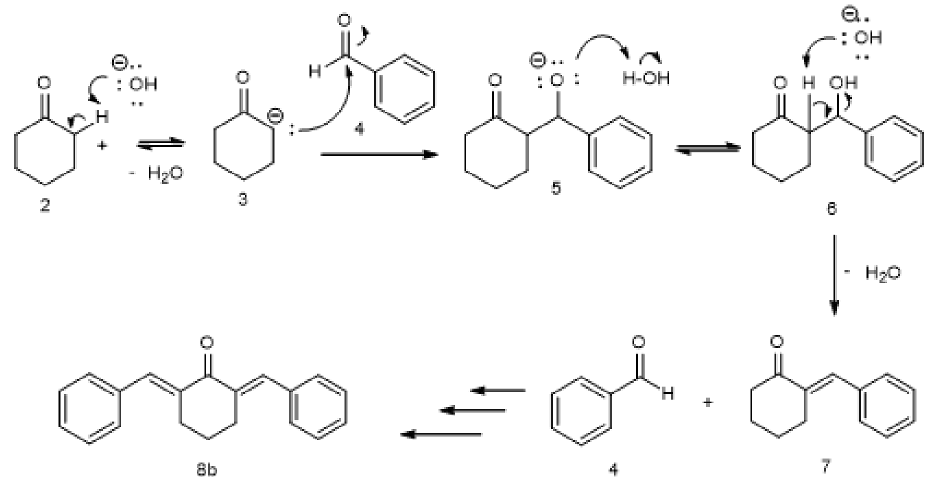
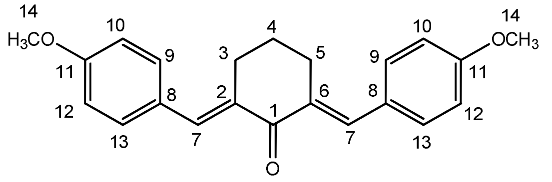


Fig 5. Synthesis of dibenzylidenecyclohexanone mechanism

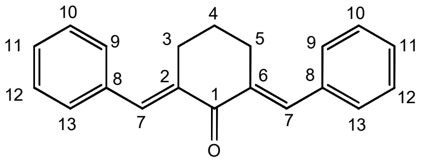
Table 1. NMR (^{1}H and ^{13}C) spectra of compound 8a (CDCl$_3$)



8a

No C	δ (∑H, m, *J* Hz) ppm	δ C (ppm)
1	-	190.2
2, 6	-	134.3
3, 5	2.92 (4H, t, 5.3)	28.5
4	1.80 (2H, m, -)	23.0
7	7.76 (2H, s, -)	136.0
8	-	128.7
9, 13	7.44 (4H, d, 7.2)	132.2
10, 12	6.93 (4H, d, 7.2)	113.8
11	-	159.9
14	3.84 (6H, s, -)	55.3

Table 2. NMR (^{1}H and ^{13}C) spectra of compound **8b** (CDCl$_3$)



8b

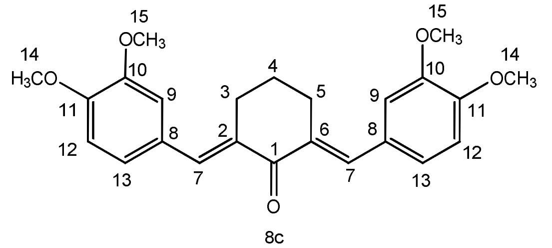
No C	δ (∑H, m, *J* Hz) ppm	δ C (ppm)
1	-	190.3
2 ,6	-	136.1
3, 5	2.93 (4H, m, -)	28.4
4	1.79 (2H, m, -)	23.0
7	7.80 (2H, s, -)	136.9
8	-	135.9
9, 13	7.46 (4H, d, 7.2)	130.3
10, 12	7.42 (4H, t, 7.2)	128.3
11	7.30 (2H, t, 7.2)	128.5

is similar to **8a** but without a singlet peak at 3.8 ppm of methoxy protons. HNMR spectra of **8c** shows a singlet peak at 7.7 ppm indicate the presence of alkene protons. Aromatic protons appeared at 7:02 ppm of singlet peak and two doublet peaks at 6.9 and 7.1 ppm. Methoxy proton indicated by two singlet peaks at 3.91 and 3.92 ppm. Methylene groups appeared at 1.8 and 2.9 ppm as a multiplet and broad triplet peak respectively.

The reaction mechanism of crossed aldol condensation of between cyclohexanone and benzaldehyde derivatives was presented on Fig. 5. The first step is the formation of a nucleophile **3** by deprotonation of Hα of cyclohexanone by the basic catalyst. Nucleophile addition of enolate **3** to the carbonyl carbon of benzaldehyde, followed with protonation would generate β-hydroxy carbonyl **6.** Benzylidenecyclohexanone **7** was formed *via* dehydration reaction towards **6**. Since there is Hα remained in the intermediate **7**, further crossed aldol condensation reaction might occur to produce dibenzylidenecyclohexanone **8b**.

Crossed aldol condensation reaction is usually performed using a conventional stirring method for a few hours and should left to stand over night. It also required large amount of solvent. To address such limitations, we have performed crossed aldol condensation between cyclohexanone and benzaldehyde derivatives to produce dibenzylidene cyclohexanones *via* MAOS method. In this study, we found that the latter method is more rapid and efficient to provide dibenzylidenecyclohexanones.

Table 3. NMR (^{1}H and ^{13}C) spectra of compound **8c** ($CDCl_3$)



8c

No C	δ (∑H, m, *J* Hz) ppm	δ C (ppm)
1	-	190.0
2, 6	-	136.0
3, 5	2.95 (4H, br t, -)	28.5
4	1.83 (2H, m, -)	23.0
7	7.75 (2H, s, -)	134.0
8	-	128.0
9	7.02 (2H, s, -)	113.0
10	-	149.0
11	-	148.0
12	6.92 (2H, d, 8.3)	110.8
13	7.12 (2H, d, 8.3)	123.8
14	3.92 (6H, s, -)	55.0
15	3.91 (6H, s, -)	55.0

CONCLUSION

In conclusion, three dibenzylidenecyclohexanones have been synthesized *via* crossed aldol condensation using MAOS method. This method has been proven to be more efficient, shorter and cleaner than stirring method.

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