

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-methoxybenzylidene)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) 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 pembandingan, 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)-benzylidenecyclopentanone **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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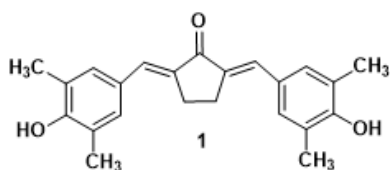


Fig 1. Structure of PGV-1

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 $NaOH/ZrO_2$ -montmorillonit 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 (1H 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 (2E,6E)-bis(4-methoxybenzylidene)cyclohexanone **8a** and (2E,6E)-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 transferred 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 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

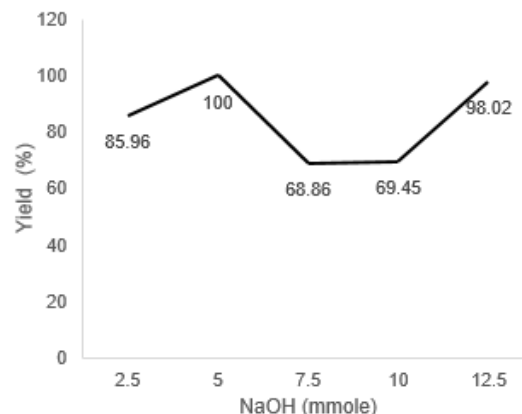


Fig 2. Optimization of NaOH catalyst of compound **8a** by MAOS method

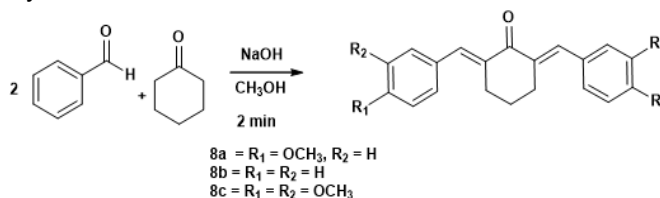


Fig 3. Crossed aldol condensation of cyclohexanone and benzaldehyde derivatives using MAOS method

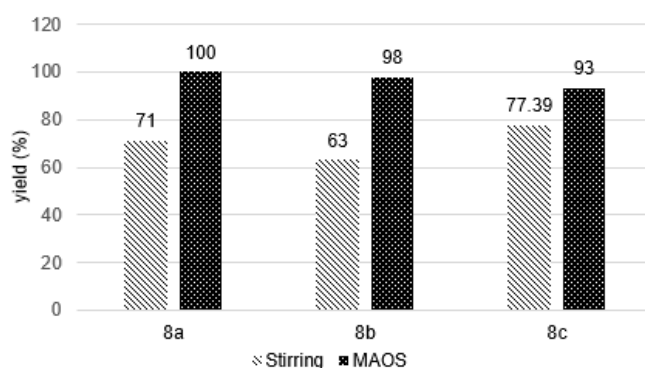


Fig 4. Comparison of the results using MAOS and stirring method

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 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**

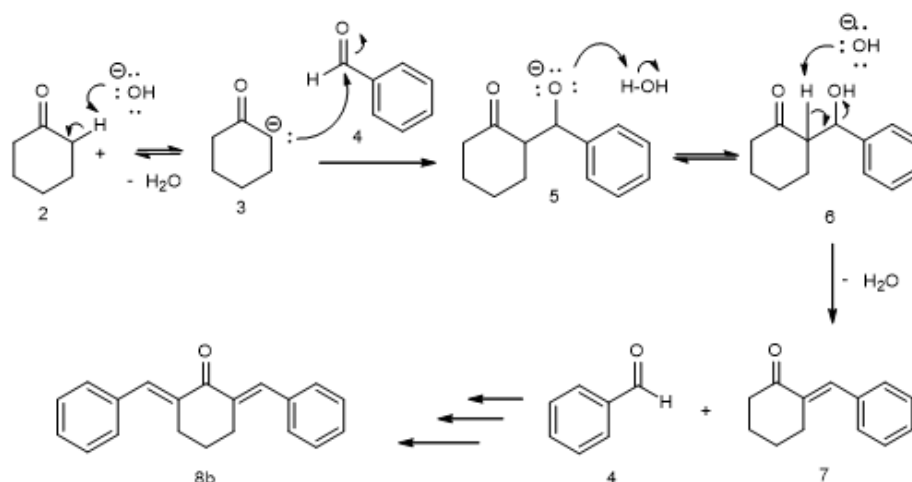


Fig 5. Synthesis of dibenzylidenecyclohexanone mechanism

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

No C	δ (ΣH , 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 (^1H and ^{13}C) spectra of compound **8b** (CDCl_3)

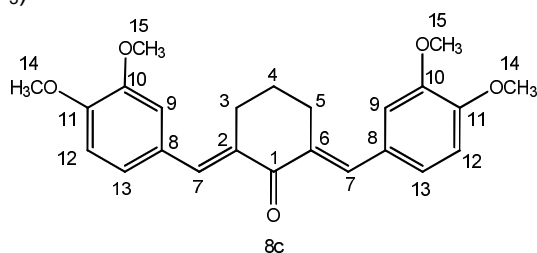
No C	δ (ΣH , m, J Hz) ppm	δ C (ppm)
1	-	190.3
2, 6	-	136.1
3, 5	2.93 (4H, m, -)	28.4
4	1.79 (2H, m, -)	23.0
7	7.80 (2H, s, -)	136.9
8	-	135.9
9, 13	7.46 (4H, d, 7.2)	130.3
10, 12	7.42 (4H, t, 7.2)	128.3
11	7.30 (2H, t, 7.2)	128.5

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 H_α 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 H_α 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 (^1H and ^{13}C) spectra of compound **8c** (CDCl_3)

No C	δ (ΣH , 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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