



The Influence of Nitro Group on Synthesis of (E) 1-(4-Methoxyphenyl)-3-phenylprop-2-en-1-one Derivatives via Claisen-Schmidt Condensation

Tutuk Budiati*

Department of Science and Pharmaceutical Chemistry, Faculty of Pharmacy, Widya Mandala Surabaya Catholic University, Indonesia

ABSTRACT

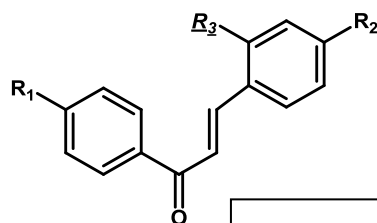
The aim of this research was to compare the synthesis of chalcone derivatives via Claisen-Schmidt condensation reaction between 4-methoxyacetophenone (1) with nitro-substituted benzaldehydes (2a-c) by conventional method and microwave irradiation assistance. The synthesized compounds were analyzed using TLC, melting point, IR and ¹H-NMR spectroscopy. The yield obtained of 4-methoxychalcone (4a) by conventional method and microwave irradiation assistance were 84% and 53% respectively. The reaction between 4-methoxyacetophenone and 4-nitro- or 2-nitro-benzaldehyde by conventional method formed 3-hydroxy-1-(4-methoxyphenyl)-3-(4-nitro-phenyl)propan-1-one (3b) and 3-hydroxy-1-(4-methoxyphenyl)-3-(2-nitrophenyl)propan-1-one (3c); the yield were 82% and 59% respectively. The presence of nitro substituent at para and ortho position on benzaldehyde caused chalcone derivative compound had not been formed yet.

Keywords: Chalcone derivatives; Nitrobenzaldehydes; Claisen-Schmidt condensation; Conventional method; Microwave irradiation assistance

INTRODUCTION

Chalcone are part of the selected group of chemical compounds associated with diverse pharmacological activities, ie. anti-inflammatory, anti-ulcerative, antibacterial, and anti-malarial activities [1-5]. They have been found in many plants as metabolic precursors of other flavonoids and isoflavonoids. From a synthetic point of view, there is a great interest for the development of structural analogues of chalcone. Chalcone can be synthesized through some reactions such as Claisen-Schmidt condensation [6] Suzuki Coupling [7], Wittig reaction [8], and Fries Rearrangement [9].

In this study, the synthesis of chalcone derivatives, namely 4-methoxychalcone (compound (4a)), 4-methoxy-4'-nitrochalcone (compound (4b)) and 4-methoxy-2'-nitrochalcone (compound (4c)), had been carried out via Claisen-Schmidt condensation using conventional method and microwave irradiation assistance to compare the results of the synthesis of the two methods. The structure of the synthesized compounds are shown in Figure 1.

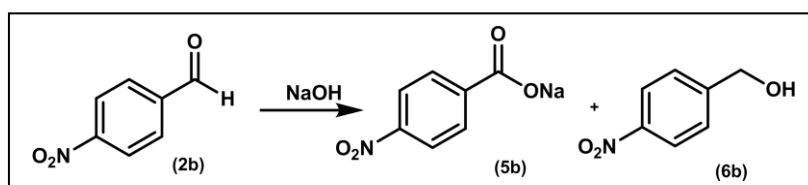


The targeted compounds:

Compound (4a) : R₁ = OCH₃, R₂ = H, R₃ = H

Compound (4b) : R₁ = OCH₃, R₂ = H, R₃ = NO₂

Compound (4c) : R₁ = OCH₃, R₂ = NO₂, R₃ = H



EXPERIMENTAL SECTION

General Procedures

All solvents, chemicals, and reagents were obtained commercially and used without purification. Purity test of the products was performed by the TLC methods on silica gel 60 F254 plates (Merck) using benzene : chloroform (2:5) as the eluent. Spot detection was performed with UV 254 nm. Melting points were measured with an Electrothermal melting point apparatus without correction. Infrared (IR) spectra were recorded in KBr pellet on a FTIR spectrophotometer (Jasco FT-IR 5300). ¹H-NMR spectra were recorded on a JEOL NMR 500 spectrometer, using TMS as internal standard.

General Synthesis of chalcones

(A) Conventional method

The procedure refers to the study of Bai et al. (2014) with modifications to the addition of the elimination step. A mixture of 4-methoxyacetophenone (1 mmol) and NaOH solution (2.5 mmol) in ethanol:water (4:1 v/v) was stirred for 5 minutes in an ice bath. To this, substituted benzaldehyde (1 mmol) was added and stirred for 1 hour at room temperature. Distilled water was added to the reaction mixture then stirred for 5 minutes, filtered, washed with distilled water until free of NaOH, and recrystallized from ethanol. The results obtained were analyzed by TLC, melting point determination, IR and ¹H-NMR spectroscopy.

(B) Microwave Irradiation Assistance

A mixture of 4-methoxyacetophenone (1 mmol) and NaOH solution (2.5 mmol) in ethanol : water (4:1 v/v) was stirred for 5 minutes in an ice bath. To this, substituted benzaldehyde (1 mmol) was added and irradiated with microwave (160 Watt, 5 minutes). Distilled water was added to the reaction mixture then stirred for 5 minutes, filtered, washed with distilled water until free of NaOH, and recrystallized from ethanol. The results obtained were analyzed by TLC, melting point determination, IR and ¹H-NMR spectroscopy.

RESULT AND DISCUSSION

Claisen-Schmidt condensation consists of two reaction steps that are nucleophilic addition, which gives the aldol product (3 a-c), and elimination [10]. The mechanism reaction of Claisen-Schmidt condensation was shown in Figure 2. Nitro substituent on benzaldehyde will decrease the electron density on the aromatic ring so that the positive charge on the carbonyl carbon atom is reduced and decrease reactivity towards nucleophilic addition.

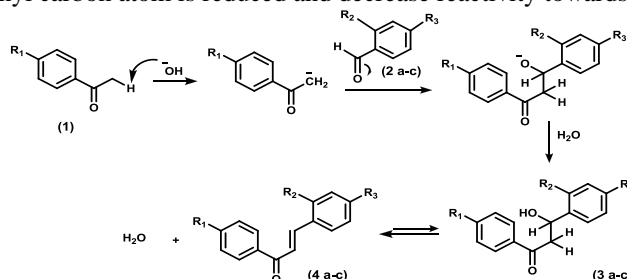


Figure 2: Reaction mechanism of synthesis chalcone derivative via Claisen-Schmidt condensation

In the present work, an attempt has been made to undertake the synthesis of compound (4a) in two step reaction: nucleophilic addition and elimination. For this purpose, the starting materials 4-methoxyacetophenone (1), benzaldehyde (2a) and NaOH solution were mixed together. Formation of the product was confirmed by a sharp band at 1654/cm due to the presence of conjugated arbonyl group along with a peak at 1259/cm for C-O stretching of -OCH₃ in IR spectra. In the ¹H-NMR spectra showed nine protons of the two benzenoid rings appear as multiplet peak at 6.94 - 8.08 ppm. Two doublet spectra of ¹H-NMR at 7.80 ppm (C2, d, 1H, J=15.7 Hz) and 7.54 ppm (C3, d, 1H, J=15.7 Hz) which indicate trans alkene form at C2-C3.

Synthesis of compound (4a) through both conventional method and microwave irradiation assistance produced white needle crystals with the yields were 84% and 53% respectively. The yield of the synthesis with microwave irradiation assistance which was smaller can be caused of the interaction between reactants' molecules was not completed yet due to the lack of the presented microwave energy.

Compound (4a): (E) 1-(4-methoxyphenyl)-3-phenylprop-2-en-1-on

White needle crystals, mp 106,0-106,5°C. IR (KBr,cm): 3055 (C-H Ar), 2935 (C-H), 1654 (C=O), 1601 and 1446 (C=C Ar), 1259 and 1027 (C-O), 973 (C-H trans), 830 (C-H para). ¹H-NMR (CDCl₃, 400 MHz) δ : 8.08-8.00 (m,

2H), 7.80 (d, 1 H, $J=15.7$ Hz), 7.70-7.59 (m, 2H), 7.54 (d, 1H, $J=15.7$ Hz), 7.47-7.34 (m, 3H), 7.02-6.94 (m, 2H), 3.89 (s, 3H).

The reaction between 4-methoxyacetophenone (1) and 4-nitrobenzaldehyde (2b) by conventional method (2.5 mmol NaOH) yielded yellow needle crystals but it was not a single compound; which shown as four spots in TLC. Therefore the synthesis procedure was modified by reducing the NaOH concentration became 0.125 mmol and resulted a single substance as white amorphous crystals. The same modification was applied to the synthesis procedure with microwave irradiation assistance but a single compound was not obtained.

A spectroscopy analysis was done to the white amorphous crystals. A sharp band at 1663/cm due to the presence of conjugated carbonyl group along with a peak at 1252/cm for C-O stretching of -OCH₃ in IR spectra. Appearance of new peaks near 1514 and 1346/cm assigning a nitro group and a peak at 831/cm showed a para substituent. A new peak also appear at 3559/cm in IR spectra and abroad peak at 4.04-3.99 ppm in ¹H-NMR spectra showed a hydroxyl group which was not shown in spectra of compound (4). In the ¹H-NMR spectra showed eight protons of the two benzenoid rings appear as multiplet peak at 6.89 - 8.26 ppm. The lack of two doublet peak at 7.80 ppm and 7.54 ppm showed that there was no trans alkene group at C2-C3. All the spectral data predicted the white amorphous crystal as compound (3b).

3-Hydroxy-1-(4-methoxyphenyl)-3-(4-nitrophenyl)propan-1-on (3b)

White amorphous crystals (81.60%), mp 117,3-117,9°C. IR (KBr./cm): 3559 and 3524 (O-H), 3082 (C-H Ar), 1663 (C=O), 1603 and 1424 (C=C Ar), 1514 and 1346 (N=O), 1252 and 1036 (C-O), 831 (C-H para). ¹H-NMR (CDCl₃, 400 MHz) δ : 8.26-8.18 (m, 2H), 7.95-7.87 (m, 2H), 7.64-7.56 (m, 2H), 6.97-6.89 (m, 2H), 5.42 (dd, 1 H, $J=9.2, 2.8$ Hz), 4.04-3.99 (br, 1H), 3.87 (s, 3H), 3.36 (dd, 1H, $J=17.7, 2.9$ Hz), 3.25 (dd, 1 H, $J=17.7, 9.2$ Hz).

The compounds' mixture in conventional method were predicted, firstly, to be the results of Claisen-Schmidt condensation that are chalcone derivative (4b) and β -hydroxyketone compounds (3b) because of the elimination step was not completed. Secondly to be the results of Cannizaro reaction between 4-nitrobenzaldehyde (2b) and NaOH that are Na 4-nitrobenzoate (5b) and (4-nitrophenyl)methanol (6b). Based on the literature, nitro substituent in the para position on benzaldehyde accelerates the rate of Cannizaro reaction 210 times at room temperature and 2200 times at 100°C compared to the unsubstituted benzaldehyde due to monoanion and dianion intermediates are stabilized [11].

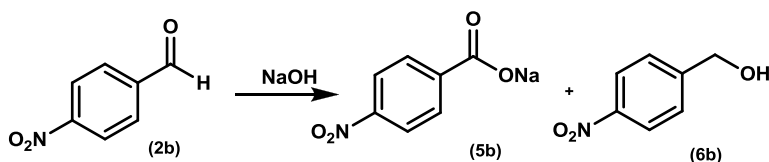


Figure 3: Cannizaro reaction of 4-nitrobenzaldehyde and NaOH

In both methods, conventional and microwave irradiation, the reaction between 4-methoxyacetophenone (1) and 2-nitrobenzaldehyde (2c) was conducted with 0.125 mmol NaOH (not 2.5 mmol NaOH) because when 2.5 mmol NaOH were used, it produced dark liquid instead of crystals. In conventional method, this procedure gives light green amorphous crystal. The same modification was applied to the synthesis procedure with microwave irradiation assistance but a single compound was not obtained. Spectroscopy analysis was done to the light green amorphous crystal and the spectral data was very similar with compound (3b) except the position of nitro group. So, the light green amorphous crystal was predicted as compound (3c) (Figure 3).

3-Hydroxy-1-(4-methoxyphenyl)-3-(2-nitrophenyl)propan-1-on (3c)

Light green amorphous crystals (59.25%), mp 138.5-139,0°C. IR (KBr./cm): 3410 (O-H), 1600 and 1433 (C=C Ar), 3010 (C-H Ar), 2943 (C-H), 1654 (C=O), 1259 and 1027 (C-O), 810 (C-H para), 1519 and 1352 (N=O), 750 (C-H ortho). ¹H-NMR (CDCl₃, 400 MHz) δ : 8.01-7.89 (m, 4H), 7.68 (s, 1H), 7.45 (ddd, 1 H, $J=8.6, 7.4, 1.5$), 6.97-6.88 (m, 2H), 5.81 (dd, 1 H, $J=9.3, 2.1$), 4.20 (s, 1H), 3.86 (s, 3H), 3.69 (dd, 1 H, $J=17.4, 2.2$), 3.11 (dd, 1H, $J=17.4, 9.3$).

The influence of the nitro substituent in the ortho position on benzaldehyde allows Baeyer-Drewsen reaction which is the reaction for synthesis indigo compound [12]. Claisen-Schmidt condensation consists of nucleophilic addition and elimination steps while Baeyer-Drewsen reaction consists of nucleophilic addition and oxidation-reduction

cyclization steps. Those reactions are similar on the nucleophilic addition step and differ in the subsequent reaction so there is a possibility that the reaction between 4-methoxyacetophenone and 2-nitrobenzaldehyde follows nucleophilic addition on the initial step but will undergo oxidation-reduction and cyclization steps to form intermediate of indigo derivative compound. The reaction mechanism of Baeyer-Drewsen occurred at compound (3c) can be predicted as seen in Figure 4.

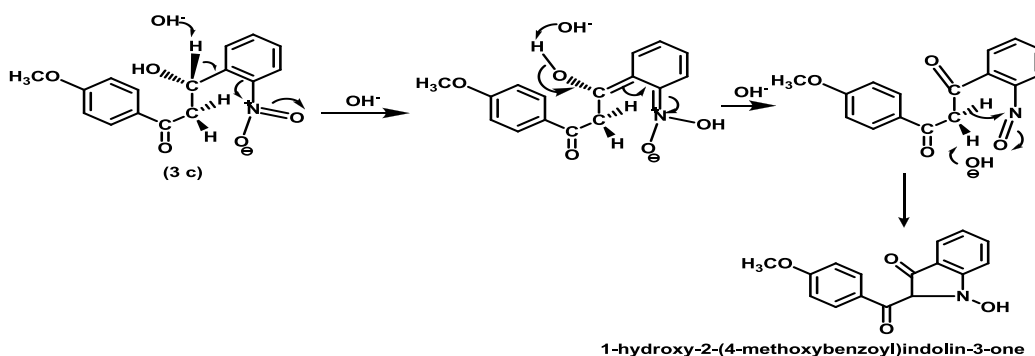
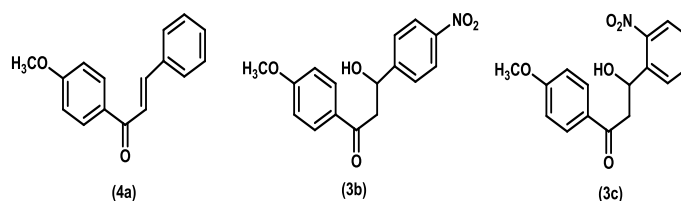


Figure 4: Several Baeyer-Drewsen reaction process

The results of structure identification of the synthesized compounds discovered that compound (4a) was chalcone derivative that was 4-methoxychalcone while the compound (3b) and (3c) were the aldol products in the synthesis of 4-methoxy-4'-nitrochalcone and 4-methoxy-2'-nitrochalcone. The formation of chalcone derivative was shown in ¹H-NMR data of compound (4a) where there were two protons in 7.80 and 7.54 ppm with coupling constant of 15.6 Hz which indicate trans alkene form, whereas those protons were not shown for compound (3b) and (3c). Instead there were three protons in the form of double doublets in 3.25, 3.36 and 5.42 ppm for compound (3b) and 3.11, 3.69 and 5.81 ppm for compound (3c) with coupling constants that had been shown on the experimental data. The structure of the synthesized compounds are shown in Figure 5.



(4a) : 4-methoxychalcone = ((E)-1-(4-methoxyphenyl)-3-phenylprop-2-en-1-one)
 (3b) : 3-hydroxy-1-(4-methoxyphenyl)-3-(4-nitrophenyl)propan-1-one
 (3c) : 3-hydroxy-1-(4-methoxyphenyl)-3-(2-nitrophenyl)propan-1-one

Figure 5: The structure of the synthesized compounds

Formation of compound (4a) occurred via nucleophilic addition step which initiated by the formation of carbanion and followed by an attack on the carbonyl carbon atom on benzaldehyde and then terminated by elimination step where hydroxyl group of β -hydroxyketone was released due to the presence of base and water to form 4-methoxychalcone compound (Figure 2). The formation of compound (3b) and (3c) only occurred via nucleophilic addition step to form aldol products which had not undergone elimination step to form chalcone derivative compounds due to the lack of base concentration. The reaction conditions and the products observed can be seen in Table 1.

On the other hand, if the nitro is the substituent of acetophenone, the Claisen-Schmidt condensation can be done with high yield [5].

Table 1: Reaction condition and products observed on synthesis of 4-methoxychalcone derivatives

Acetophenone	Benzaldehydes	NaOH		Product	
				Compound	Mp (°C)
-1	(2a-c)				
<i>Conventional method</i>					
1 mmol	(2a) : 1 mmol	2.5 mmol		(4a); 84%	106
1 mmol	(2b); 1 mmol	2.5 mmol		mixture	
1 mmol	(2b); 1 mmol		0.125 mmol	(3b): (82%)	117
1 mmol	(2c); 1 mmol	2.5 mmol		Dark liquid	
1 mmol	(2c); 1 mmol		0.125 mmol	(3c): (59%)	139
<i>Microwave Irradiation Assistance</i>					
1 mmol	(2a) : 1 mmol	2.5 mmol		(4a); 53%	106
1 mmol	(2c); 1 mmol		0.125 mmol	Crystal not formed	
1 mmol	(2c); 1 mmol		0.125 mmol	Crystal not formed	

CONCLUSION

The presence of nitro group as substituent of benzaldehydes (2b-c) caused Claisen-Schmidt condensation cannot occurred using base as a catalyst. It is prefer to do the Claisen-Schmidt condensation in acid catalyst. It is not recommended to use microwave-assisted irradiation in the synthesis of chalcone derivatives if a nitro substituent is present.

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