

Facile and Rapid Synthesis of Arylidene Derivatives by Microwave Assisted NH_4OAc Catalyzed under Solvent Free Condition

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Abstract

In this present study, we described an efficient and green procedure for the ammonium acetate (NH_4OAc) catalyzed microwave assisted Knoevenagel condensation for the synthesis of arylidene derivatives. A series of arylidene derivatives viz 3a-3g were synthesized with the condensation reaction of active methylene compounds such as ethyl cyanoacetate, benzoyl acetone, methyl acetoacetate 2a-2g with corresponding aromatic and heterocyclic aldehydes 1a-1g under solvent free condition. Variety of functional groups such as bromo, fluoro, cyano, methyl, methoxy and nitro were survived under the reaction conditions. The structure of the products has been established on the basis of their IR, ¹H NMR, ¹³C NMR and Mass spectroscopic data analyses. The antibacterial activity against two bacteria such as *Klebsiella oxytoca* and *Escherichia coli* has been studied and it was found that the synthesized compounds were found to inhibit the growth of the pathogenic bacteria.

Keywords: Knoevenagel condensation; Aldehydes; Arylidene acrylate; Ethylcyanoacetate; Ammonium acetate; Solvent free; Microwave irradiation

Introduction

Many chemical processes employ large amount of hazardous and toxic solvents. The choice of pursuing aqueous reactions is becoming more important and urgent than ever before, due to its environmental impact and cost of chemical processes [1]. Organic reactions under solvent free conditions have increasingly attracted chemists' interests particularly from the viewpoint of green chemistry [2-4]. The Knoevenagel condensation between aldehyde and active methylene compounds is an important reaction in organic synthesis in forming C=C double bonds. It has been used for the preparation of a range of substituted alkenes and bioactive molecules and as a key step in natural product synthesis. In general, the Knoevenagel condensation is carried out using organic bases such as aliphatic amines, urea, ethylenediamine and piperidine or their corresponding ammonium salts, and the amino acids glycine [5,6]. Among these catalysts the ammonium salt such as NH_4OAc is another inexpensive, available, efficient and mild catalyst for the synthesis of Knoevenagel condensation of arylidene derivatives. The Knoevenagel condensation has been receiving considerable attention, due to its broad spectrum of uses including cosmetic, perfume, agrochemicals and pharmaceuticals application [7]. In the last ten years, a lot of methods to achieve Knoevenagel condensation are known. For example, some novel heating methods such as microwave irradiation, had been applied in Knoevenagel condensation [8]. Meanwhile, accumulating efforts have been made to explore novel catalysts for Knoevenagel reaction [9,10]. However, some of these methods suffer from some drawbacks such as long reaction time, the uses of harmful catalyst, lots of solvent and

energy expense. Microwave promoted organic synthesis is a fast, efficient method of heating a system in order to achieve the completion of a desired reaction. Microwave promoted organic synthesis can help to produce high yields of products in a short time, while reducing side reactions and making reaction easier. The syntheses of some arylidenemalonitriles by the reaction of malonitriles and aldehydes as well as synthesis of selective acrylate by condensation reaction have also been reported [11,12].

The present work, therefore, is to synthesis of Knoevenagel condensation of various aromatic aldehydes with active methylene compounds using NH_4OAc as catalyst under solvent free condition.

Experimental Methods and Materials

All chemicals were received from commercial sources (Sigma-Aldrich and Merck, Germany) and were used without further purification.

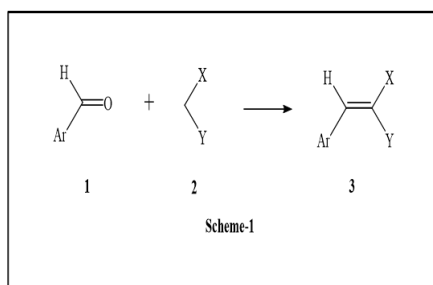
Synthesis and characterization of acrylates

The reaction was carried out in a 50.0 mL beaker in which an equimolecular mixture of aromatic aldehyde 1 and active methylene compound 2 (1:1) were added in a catalytic amount of ammonium acetate (NH_4OAc). All the reaction scales were same, such as 2.0 mmol of each starting material and 0.25 mmol catalyst. For example, a mixture of 4-bromobenzaldehyde (2.0 mmol), ethyl cyanoacetate (2.0 mmol) and ammonium acetate (0.25 mmol) was placed in a pyrex glass 50.0 mL beaker. The reaction mixture was mixed thoroughly with the help of a glass rod. The mixture was then subjected to microwave irradiation at 300-800 W for the reaction period of 1~3 minutes. The progress of the reaction was followed by thin layer chromatography (TLC) (hexane:ethyl acetate, ratio:4:1). After completion of the

reaction, it was cooled and then the solid mass of the products was re-crystallized using ethyl acetate and n-hexane solvent mixture. The reaction process is shown in Scheme 1.

All the compounds showed a single spot on the TLC plate. From these observations, therefore, it was suggested that the compounds were almost 99.0% pure.

Gallen kamp melting point apparatus was used to record the melting point of the solid compounds, the heating was done carefully to ensure a steady rise of temperature. The TLC was performed on Kieselgel GF254 and visualization was accomplished by UV light. Infrared spectra were observed on a Shimadzu FTIR- spectrometer (IR prestige 21). ^1H NMR spectra were recorded on a JEOL JNM ECS FT NMR at 400 MHz spectrometer using TMS as an internal standard. Coupling constants J are given in Hz. The mass spectra were recorded on a Jeol SX-102 (FAB) spectrometer. Analytical TLC was performed on pre-coated alumina sheet and the product was visualized by UV light. All the reactions were carried out in a domestic microwave oven (Samsung, MW76ND).



Scheme 1: Ethyl acetate and n-hexane solvent mixture.

Antibacterial activity assay

The antibacterial activity assay was performed by disc diffusion method [13] with little modification against two Gram-negative bacteria such as: (i) *Klebsiella oxytoca* and (ii) *Escherichia coli* at the concentration of 60-200 $\mu\text{g}/\text{disc}$, which is a qualitative to semi quantitative test. Briefly, 6.0 mm diameter and 1.0 mm thickness normal Whitman filter paper no.1 was used as sample disc. The compounds (2.0 mg) to be tested were dissolved in methanol (2 mL). The concentration used in this study was 1.0 mg/mL of each sample. The completely dried filter paper discs were placed on the surface of the seeded agar medium in triplicate tests for each sample. Plates were allowed to stand for 2 h for complete diffusion. Then, the plates were incubated at 37°C for 24 h to 48 h, after which the susceptibility of each organism to each sample was estimated by measuring the diameter of the zones of inhibition. The plate with sample and antibiotic was kept in incubator and observed the result after 24 h. Sometimes it may necessary to keep it for 48 h. Gentamycin was used as the standard. The results of the activity test are shown in Table 1.

Compound s SL no.	Compounds name	Zone of inhibition (mm)			
		Klebsiell a oxytoca	Standar d	Escherichia coli	Standar d

3a	Ethyl-2-cyano-3-(4-bromophenyl) acrylate	--	--	6	11
3b	Ethyl-2-cyano-3-(4-fluorophenyl) acrylate	6	7	--	--
3c	Ethyl-2-cyano-3-(4-pyridinphenyl) acrylate	6	17	7	27
3d	Ethyl-2-cyano-3-(4-methylphenyl) acrylate	6	6	8	25
3e	2-(4-fluorobenzylidene)-1-phenylbutane-1,3-dione	5	6	--	--
3f	Methyl-2-(4-fluorobenzylidene)-3-oxobutanoate	6	6	7.5	25
3g	Methyl-2-(4-nitrobenzylidene)-3-oxobutanoate	--	--	--	--

Key: "--" means inactive against used bacteria.

Table 1: Antibacterial activity for the synthesized compounds. Gentamycin was used as standard.

Characterization

In general, the reactions were clear and free from the Michael adduct. All the products were characterized by ^1H -NMR, ^{13}C -NMR, IR and Mass spectroscopic data analyses. The ^1H NMR spectra of the products 3a-3i showed the olefinic proton around δ 7.5-9 ppm (in CDCl_3) as singlet peak. In the IR spectrum, the absorption peak observed at $1703\text{-}1727\text{ cm}^{-1}$ due to the carbonyl, and the band at $2213\text{-}2221\text{ cm}^{-1}$ is due to the $-\text{CN}$ groups. Our results are in good agreement with reported value [14-16]. The spectroscopic data of all the products are given below sequentially. All the FT-IR, ^1H -NMR, ^{13}C -NMR, and Mass spectroscopic data are given as supporting information (SI).

Ethyl 2-cyano-3-(4-bromophenyl) acrylate (3a): Yield 87% (322.0 mg), white crystals, $R_f=0.68$ (in EtOAc/Hexane: 0.5:4.5), (99.0% pure), Mp: $90\sim 92^\circ\text{C}$. IR (KBr) $\nu_{\text{max}}(\text{cm}^{-1})$: 3031 (aromatic=C-H), 2985 (alkene=C-H) 2221 ($\text{C}\equiv\text{N}$), 1719 ($\text{C}=\text{O}$), 1611 ($\text{C}=\text{C}$). ^1H NMR δ ppm 8.17 (s, 1H), 7.86 (d, 2H, $J=8.8$ Hz), 7.65 (d, 2H, $J=8.4$ Hz), 4.37 (q, 2H, $J=7.2$ Hz), 1.39 (t, 3H, $J=7.2$ Hz). ^{13}C NMR (CDCl_3) δ ppm 162.1, 153.4, 132.6, 132.2, 130.2, 128.2, 115.2, 103.6, 62.8, 14.1. Mass (m/z): 280, 154, 137, 89, 39. $\text{MF}=\text{C}_{12}\text{H}_{10}\text{O}_2\text{BrN}$.

Ethyl 2-cyano-3-(4-fluorophenyl) acrylate (3b): Yield 82% (203.0 mg), $R_f=0.87$ (in EtOAc/Hexane: 1:4), white crystals, (99.0% pure), Mp: $80\sim 82^\circ\text{C}$. IR (KBr) $\nu_{\text{max}}(\text{cm}^{-1})$: 3108 (aromatic=C-H), 2993 (alkene=C-H), 2845, 2221 ($\text{C}\equiv\text{N}$), 1719 ($\text{C}=\text{O}$), 1611 ($\text{C}=\text{C}$). ^1H NMR δ ppm 8.19 (s, 1H), 8.01 (m, 2H, $J=5.6$ Hz), 7.18 (m, 2H, $J=8.4$ Hz), 4.37 (q, 2H, $J=7.6$ Hz), 1.38 (t, 3H, $J=6.8$ Hz). ^{13}C NMR (CDCl_3) δ ppm 162.3, 134.2, 134.1, 132.4, 127.8, 117.7, 117.0, 116.4, 62.7, 14.0. Mass (m/z): 220, 137, 136, 89, 39. $\text{MF}=\text{C}_{12}\text{H}_{10}\text{O}_2\text{FN}$.

Ethyl 2-cyano-3-(4-pyridinphenyl) acrylate (3c): Yield 96% (206.0 mg), $R_f=0.68$ (in EtOAc/Hexane: 0.5:4.5), brown crystals, (99.0% pure), Mp: 175~177°C. IR (KBr) $\nu_{\text{max}}(\text{cm}^{-1})$: 3039 (aromatic C-H), 3000 (alkene=C-H), 2221 ($\text{C}\equiv\text{N}$), 1727 ($\text{C}=\text{O}$), 1619 ($\text{C}=\text{C}$). ^1H NMR δ ppm 8.18 (s, 1H), 8.81 (d, 2H, $J=6.4$ Hz), 7.74 (d, 2H, $J=6.4$ Hz), 4.41 (q, 2H, $J=7.2$ Hz), 1.41 (t, 3H, $J=7.2$ Hz). ^{13}C NMR (CDCl_3) δ ppm 161.2, 152.0, 151.0, 138.0, 123.2, 114.2, 108.3, 63.3, 14.0. Mass (m/z): 203, 175, 131, 89, 39. $\text{MF}=\text{C}_{11}\text{H}_{10}\text{O}_2\text{N}_2$.

Ethyl 2-cyano-3-(4-methylphenyl) acrylate (3d): Yield 96% (231.0 mg), $R_f=0.48$ (in EtOAc/Hexane: 1:4), white powder, (99.0% pure), Mp: 88~90°C. IR (KBr) $\nu_{\text{max}}(\text{cm}^{-1})$: 3031 (aromatic C-H), 2993 (alkene=C-H), 2213 ($\text{C}\equiv\text{N}$), 1727 ($\text{C}=\text{O}$), 1600 ($\text{C}=\text{C}$). ^1H NMR δ ppm 8.30 (s, 1H), 7.93 (d, 2H, $J=8.4$ Hz), 7.37 (d, 2H, $J=8.4$ Hz), 4.29 (q, 2H, $J=7.2$ Hz), 1.28 (t, 3H, $J=7.2$ Hz), 2.35 (s, 3H). ^{13}C NMR (CDCl_3) 162.5, 155.4, 144.9, 131.5, 130.5, 130.0, 129.2, 116.6, 21.8, 14.5. Mass (m/z): 216, 170, 137, 91, 43. $\text{MF}=\text{C}_{13}\text{H}_{13}\text{O}_2\text{N}$.

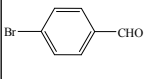
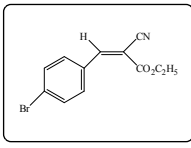
2-(4-fluorobenzylidene)-1-phenylbutane-1,3-dione (3e): Yield 95% (236.0 mg), $R_f=0.75$ (in EtOAc/Hexane: 1:4), light yellow crystal, (99.0% pure), Mp: 108~110°C. IR (KBr) $\nu_{\text{max}}(\text{cm}^{-1})$: 3101 (aromatic C-H), 2946 (alkene=C-H), 2840 ($-\text{CH}_3$), 1703 ($\text{C}=\text{O}$), 1649 ($\text{C}=\text{C}$). ^1H NMR δ ppm 7.75 (s, 1H), 7.90 (m, 2H), 7.55 (m, 1H), 7.41 (m, 2H), 7.33 (m, 2H), 7.91 (m, 2H), 2.37 (s, 3H). ^{13}C NMR (CDCl_3) δ ppm 197.9, 195.5, 164.9, 162.4, 139.7, 139.2, 135.8, 134.2, 132.4, 132.3, 129.1, 129.0, 116.1, 115.9, 27.2. Mass (m/z): 269, 105, 77, 43. $\text{MF}=\text{C}_{17}\text{H}_{13}\text{O}_2\text{F}$.

Methyl 2-(4-fluorobenzylidene)-3-oxobutanoate (3f): Yield 78% (194.0 mg), $R_f=0.40$ (in EtOAc/Hexane: 1:4), light yellow crystal, (99.0% pure), Mp: 156~158°C. IR (KBr) $\nu_{\text{max}}(\text{cm}^{-1})$: 3078 (aromatic C-H), 3039 (alkene=C-H), 2993 ($-\text{CH}_3$), 1719 ($\text{C}=\text{O}$), 1680 ($\text{C}=\text{C}$). ^1H NMR δ ppm 8.91 (s, 1H), 7.14 (m, 2H), 7.01 (m, 2H), 7.41 (m, 2H), 3.54 (s, 3H), 2.59 (s, 3H). ^{13}C NMR (CDCl_3) δ ppm 167.8, 162.3, 159.9, 146.3, 144.5, 129.2, 115.2, 102.0, 51.2, 18.7. $\text{MF}=\text{C}_{12}\text{H}_{11}\text{O}_3\text{F}$.

Methyl 2-(4-nitrobenzylidene)-3-oxobutanoate (3g): Yield 76% (230.0 mg), $R_f=0.25$ (in EtOAc/Hexane: 1:4), yellow crystal, (99.0% pure), Mp: 125~127°C. IR (KBr) $\nu_{\text{max}}(\text{cm}^{-1})$: 3104 (aromatic C-H), 3047 (alkene=C-H), 2954 ($-\text{CH}_3$), 1743 ($\text{C}=\text{O}$), 1657 ($\text{C}=\text{C}$). ^1H NMR δ ppm 8.21 (m, 2H), 7.69 (s, 1H), 7.57 (m, 2H), 3.82 (s, 3H), 2.44 (s, 3H). ^{13}C NMR (CDCl_3) δ ppm 193.8, 187.2, 148.4, 139.0, 137.8, 130.2, 129.8, 123.9, 52.8 and 26.8. $\text{MF}=\text{C}_{12}\text{H}_{11}\text{O}_5\text{N}$.

Results and Discussion

We have synthesized seven compounds on the NH_4OAc catalyzed condensation of the active methylene compounds with the aromatic and heterocyclic aldehydes (Scheme 1). The structure of the products, substrate, yield of % are shown in Table 2.

Entry	Aldehyde	Product	Watt/Time (second)	Yield (%)
1a		 (3a)	300/60	87

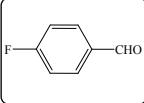
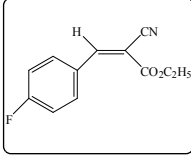
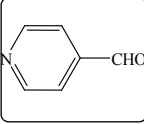
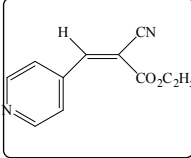
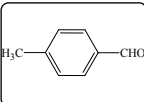
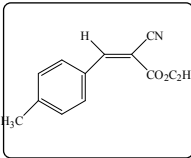
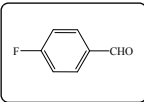
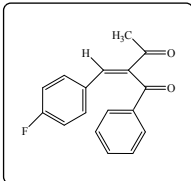
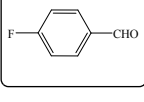
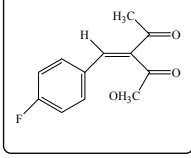
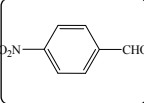
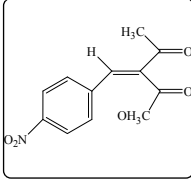
1b		 (3b)	300/60	82
1c		 (3c)	450/120	96
1d		 (3d)	450/60	96
1e		 (3e)	600/180	95
1f		 (3f)	800/120	78
1g		 (3g)	450/180	76

Table 2: Structure of the aldehydes, products, % yield and melting points of the microwave assisted Knoevenagel condensation reaction of various aromatic aldehydes and active methylene compounds.

The reaction of p-bromobenzaldehyde with ethyl cyanoacetate in presence of catalytic amount of ammonium acetate under microwave irradiation resulted in the formation of ethyl-2-cyano-3-(4-bromophenyl) acrylate (3a) in 87% yield under solvent free condition. In a similar manner, a wide range of aldehydes including aromatic and heterocyclic reacts efficiently with the active methylene compounds 2 under same reaction condition to give the arylidene derivatives with yield% of 96 to 76. The structures are established based on FT-IR, ^1H NMR, ^{13}C NMR and MS spectroscopic analyses shown in Table 2.

The results representing antimicrobial activity of the synthesized compounds presented in Table 1. The activity of three typical independent compounds such as 3b, 3c and 3d are shown in Figure 1. From the antimicrobial activity test results, it has been observed that almost all the compounds except 3g showed the moderate antibacterial activity against the used pathogens. The highest activity 6.0 mm of zone of inhibition was found to have against *K. oxytoca* for the compounds 3b, 3c, 3d and 3f and the lowest activity 5.0 mm was found to be for the compound 3e. The compounds 3a and 3g were found to be inactive against the pathogen *K. oxytoca*. On the contrary, four compounds, out of seven, such as 3a, 3c, 3d and 3f were found to be active against the pathogen *E. coli* whereas compounds 3b, 3e and 3g were inactive against *E. coli*. The highest activity 8.0 mm of zone of inhibition was observed for the compound 3d and the lowest activity 7.0 mm of zone of inhibition was observed for the compound 3c. The compound 3g was found to be inactive in both the used pathogens. This might be due to the structure-activity relationship of the compound 3g, since, it contains two electron-donating groups (CH_3O -, $-\text{CH}_3$) and one strong electron-withdrawing group ($-\text{NO}_2$). These differences in electronic properties might produce difference in antibacterial susceptibility and are inactive against Gram-negative pathogens (*K. oxytoca* and *E. coli* are both Gram-negative) [17]. However, the synthesized compounds are recommended as antibacterial agents.

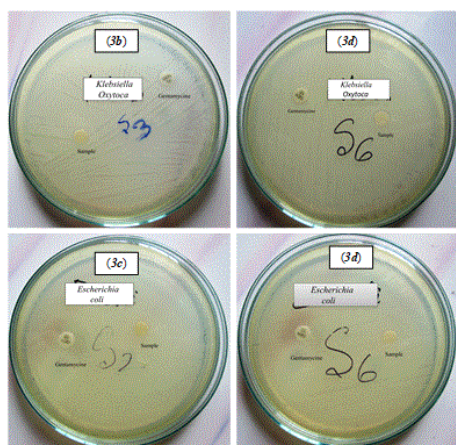


Figure 1: Zone of inhibition of antibacterial activity against *Klebsiella oxytoca* and *Escherichia coli* for three typical synthesized compounds 3b, 3c and 3d. Gentamycin was used as standard.

Conclusion

In conclusion, we have synthesized seven arylidene derivatives by microwave irradiation using NH_4OAc as catalyst under solvent free condition. This method could be applied to a wide range of aldehydes including aromatic and heterocyclic substrates. The advantages of this method are high yields, relatively short reaction times and low cost, simple experimental and isolation procedures. Six compounds, out of seven, were found to be moderate active against Gram-negative pathogenic bacteria. Finally, it is in agreement with the green chemistry protocols.

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