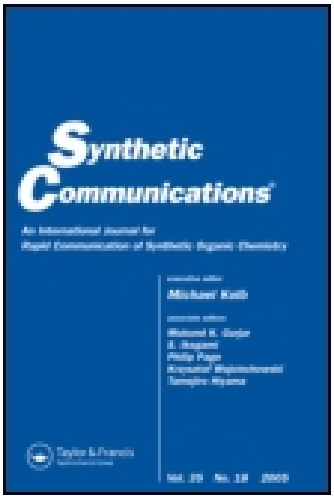

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Effect of Microwave Irradiation on Reaction of Arylaldehyde Derivatives with Some Active Methylene Compounds in Aqueous Media

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Abstract: The effect of microwave irradiation on the condensation reactions of arylaldehydes **1** and active methylene compounds **2** in aqueous media was studied and compared with "classical" conditions. The results show that the condensation was carried out only under microwave irradiation in the presence of ammonium chloride as a catalyst, followed by dehydration, to afford (E)-olefins **3**. The protocol was used to synthesize coumarins by a condensation reaction of salicylaldehyde or its derivatives with various derivatives of ethylacetate **5** (*e.g.*, $R^3CH_2CO_2Et$; R^3: CO_2Et, CO_2Me, COMe, CN) in high yields. These investigations will contribute to the development of environmentally friendly and inexpensive processes in organic synthesis.

Keywords: Aqueous media, coumarin, MW irradiation

Chemical processes employ large amounts of hazardous and toxic solvents. The choice of pursuing a clean and inexpensive aqueous reaction medium,

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to minimize the economic cost and environmental impact of a chemical process, is becoming ever more urgent for the future.

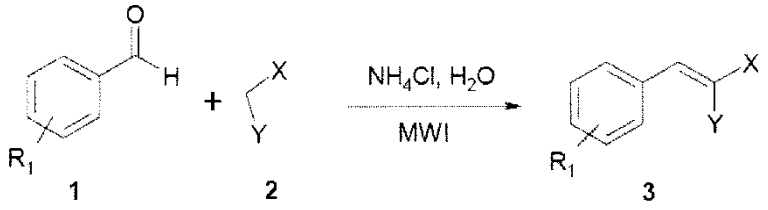
Organic reactions under solvent-free[1,2] and aqueous[3–5] conditions have increasingly attracted chemists' interests, particularly from the viewpoint of green chemistry.[6] As an important carbon–carbon bond-forming reaction, condensation reactions have been extensively studied. Generally, this type of reaction is catalyzed by a base or Lewis acid in the liquid-phase system. In recent years, chemists paid more and more attention to the clean synthesis of alkenes by condensation reactions. Recently, several methods based on a solid-phase synthesis utilizing Kneovenagel condensation for preparation of coumarins have been reported.[7–9] These methods have their own merits and disadvantages; therefore, the introduction of efficient and new methods based on green methodology is still in demand.

Microwave irradiation has been utilized as one of the most convenient and efficient ways to promote organic reactions.[10,11] Recently, we have reported the MgO-catalyzed Knoevenagel condensation in solventless system.[12] Armed with these experiments, we report herein the condensation reaction of arylaldehydes **1** with active methylene compounds **2** in aqueous media under microwave irradiation.

We utilized the microwave-irradiation technique to promote the solvent-free synthesis of coumarins *via* piperidine-catalyzed Knoevenagel condensation of salicylaldehydes with active methylene compounds in high yields.[13] The aim of this work was to study the same condensation reactions in the presence of aqueous-soluble basic catalysts such as KOH, NaOH, and K_2CO_3 *via* "classical" heating and under microwave irradiation in aqueous media.

We began our studies with conventional refluxing of arylaldehyde in water with nitroacetonitrile and the adequate KOH. After several hours, refluxing the reaction did not proceed at various temperatures after a long reaction time (12–24 h). Thus to speed reaction times, we used microwave heating of the reaction mixture. We used a domestic microwave oven, and the reactions were carried in a beaker. The irradiation was paused every minute for an interval of 20 sec so as to prohibit very high temperatures. The monitoring of the reaction by Thin Layer Chromatography (TLC) in the different solvent systems, visualizing spots with UV lamp or iodine vapor, show that in no case the reaction did proceed. The addition of catalytic amount of tetrabuthylammoniumbromide as a Phase Transfer Catalyst (PTC) to the mixture had no effect on the progress of the reaction.

Ammonium chloride was added as a catalyst to the mixture of reactants in aqueous media and the mixture was subjected to microwave irradiation. The monitoring of the reaction by TLC show that the condensation reaction proceeded in this condition (Scheme 1). Furthermore, the use of ammonium chloride in water was sufficient to promote the reaction and no additives such as KOH, NaOH, or K_2CO_3 were required for this reaction. The use of



Scheme 1.

salicylaldehyde derivatives **4** in this reaction with ethylacetate derivatives **5** afforded to 3-substitutedcoumarins **6** in good yields (Scheme 2).

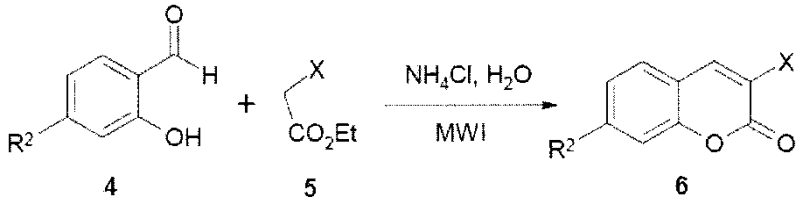
In summary, this method describes a noticeable improvement in Knoevenagel condensations and synthesis of 3-substitutedcoumarins by the Knoevenagel condensation and takes advantage of both aqueous media reaction and microwave activation. As is shown in Tables 1 and 2, the reaction time is reduced to only a few minutes by using microwave dielectric heating. The reactions can be run safely in good yields.

EXPERIMENTAL

All of the melting points were determined on an Electrothermal 9100 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer model 843. ^{1}H-NMR (Proton nuclear magnetic resonance) spectra were recorded on a Bruker Avance 500 MHz or JEOL FX90 MHz instruments. Mass spectrum was obtained on a Shimadzu QP 1100EX instrument. Analytical calculation was obtained on a LECO CHNO-932 Analyzer instrument.

GENERAL PROCEDURE

Arylaldehyde (20 mmol), activated methylene compound (22 mmol), and excess ammonium chloride were mixed in water thoroughly. The mixture



Scheme 2.

Table 1. Reaction of arylaldehydes **1** with active methylene compounds **2** in water to give products **3**

Entry	R^1	X	Y	Time (min)	M (°C)	Yield (%)
a	4-SMe	NO_2	CN	2.5	115–117	85
b	4-Me	NO_2	CN	2	94–96	87
c	4-OH	NO_2	CN	3	215–218	90
d	2-OMe	NO_2	CN	3	129–131	80
e	3-OMe	NO_2	CN	2	118–120	70
f	4-Cl	NO_2	CN	2.5	115–117	92
g	H	CO_2H	CO_2H	3	193–194	85
h	4-Me	CO_2H	CO_2H	2.5	201–203	87
i	2-Cl	CO_2H	CO_2H	3	191–193	88

was placed in a household microwave oven. The progress of reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was then allowed to cool to room temperature and, after addition of water, was extracted with ethylacetate and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure and the resulting crude product was subjected to column chromatography using hexane/AcOEt as solvent to obtain related products (Table 1 and Table 2).

SELECTED SPECTROSCOPIC DATA

3a: ^{1}HNMR δ ($CDCl_3$): 2.55 (s, 3H, Me), 7.34 (br d,H, *J* 8.8 Hz, aromatic), 7.90 (br d, 2H, *J* 8.8 Hz, aromatic), 8.55(s, 1H, H-2). ^{13}C NMR (CD3COCD3): δ 14.2, 112.4, 122.4, 124.3, 126.2, 133.2, 148.9, 151.4. MS: m/z (%) 220 (98, M+), 174 (100), 173 (52), 159 (64), 127 (47). Anal. calc. for $C_{10}H_8N_2O_2S$ (220): C, 54.53; H, 3.66; N, 12.72. Found: C, 54.48; H, 3.67; N, 12.66%.

Table 2. Preparation of coumarins **6** *via* Knoevenagel reaction in water

Entry	R^2	X	Time (min)	M (°C)	Yield (%)
a	OH	CO_2Et	3	173–175	82
b	OH	CO_2Me	3	264–267	85
c	OH	CN	2.8	249–251	87
d	H	COMe	3	115–118	79
e	H	CO_2Et	2.5	94–97	80

3b: ^{1}HNMR δ (CDCl3): 2.51 (s, 3H, Me), 7.40 (br d, 2H, *J* 8.8 Hz, aromatic), 7.92 (br d, 2H, *J* 8.8 Hz, aromatic), 8.63 (s, 1H, H-2). ^{13}C NMR (CD3COCD3) δ 21.8, 112.1, 123.2, 125.9,131.0, 132.8, 147.8, 149.2. MS: m/z (%) 188 (50, M+), 141 (45), 140 (61), 115 (100), 103 (53). Anal. calc. for $C_{10}H_8N_2O_2$ (188): C, 63.82; H, 4.28; N, 14.89. Found: C, 63.90; H, 4.93; N, 14.87%.

3c: ^{1}HNMR δ (CD3COCD3): 7.11 (br d, 2H, *J* 8.8 Hz, aromatic), 8.12 (br d, 2H, *J* 8.8 Hz, aromatic), 8.78 (*s*, 1H, H-2), 9.97 (br s, 1H, OH-phenolic). ^{13}C NMR (CD3COCD3) δ 112.2, 117.3, 119.5, 120.1, 135.8, 148.7, 164.9. MS: m/z (%) 190 (62, M+), 144 (54), 143 (100), 116 (47), 89 (100). Anal. calc. for $C_9H_6N_2O_3$ (190): C, 56.85; H, 3.18; N, 14.73. Found: C, 56.78; H, 3.25; N, 14.66%.

3d: ^{1}HNMR δ (CDCl3): 4.01 (s, 3H, OMe), 6.97–8.31 (m, 4H, aromatic), 9.21 (s, 1H, H-2). ^{13}C NMR (CD3COCD3) δ 55.8, 111.4, 112.3, 116.5, 121.2, 123.2, 129.6, 137.6, 142.4, 160.6. MS: m/z (%) 204 (100, M+). 157 (65), 143(87), 115 (46), 103 (65). Anal. calc. for $C_{10}H_8N_2O_3$ (204): C, 58.82; H, 3.95; N, 13.72. Found: C, 58.92; H, 3.94; N,13.87%.

3e: ^{1}HNMR δ (CDCl3): 3.88 (s, 3H, OMe), 7.22–7.60 (m, 4H, aromatic), 8.62 (s, 1H, H-2). ^{13}C NMR (CD3COCD3) δ 55.7, 111.8, 116.6, 121.8, 124.1, 125.3, 129.6, 131.5, 149.2, 160.7. MS: m/z (%) 204 (100, M+). 143 (61), 115(65). Anal. Calc. for $C_{10}H_8N_2O_3$ (204): C, 58.82; H, 3.95; N,13.72. Found: C, 58.88; H, 3.87; N, 13.64%.

3f: ^{1}HNMR δ (CDCl3): 7.54–8.11 (m, 4H, aromatic), 8.65 (s, 1H, H-2). ^{13}C NMR (CD3COCD3) δ 110.8, 123.6, 126.6, 129.7, 133.2, 140.6, 147.1. MS: m/z (%) 208 (55, M+), 161 (85), 127 (100), 75 (61). Anal. calc. for $C_9H_5ClN_2O_2$ (208): C, 51.82; H, 2.42; N, 13.43. Found: C, 51.88; H, 2.33; N, 13.35%.

3g: ^{1}HNMR δ ($CDCl_3$/DMSO d6): 7.35(3H, m), 7.6(1H, s, vinyl-H), 7.48 (2H, m). ^{13}C NMR ($CDCl_3$/DMSO-d6) δ 169.12, 165, 140.2, 133.7, 130.9, 130, 129.5, 128.7. IR, ν (KBr disc): 3300–2460, 1700, 1630, 1462 cm^{-1}.

3h: ^{1}HNMR δ ($CDCl_3$/DMSO d6): 2.34 (3H, s.Me), 7.03 (2H, d, J = 8.02 Hz), 7.37 (2H, d, J = 8.07), 7.42 (1H, s, vinyl-H). ^{13}C NMR ($CDCl_3$/DMSO-d6) δ 169.04, 166.1, 141.2, 140, 130.9, 130.11, 128, 21.89. IR, ν (KBr disc): 3320–2465, 1701, 1610, 1450, 1298, 1245 cm^{-1}.

3i: ^{1}HNMR δ ($CDCl_3$/DMSO d6): 7.36–7.25(2H, m), 7.4 (1H, dd, J = 7.9 and 1.4 Hz), 7.5 (1H, dd, J = 7.5 and 1.5 Hz), 7.7 (1H, s, vinyl-H). ^{13}C NMR ($CDCl_3$/DMSO-d6) δ 168, 165, 136.1, 132.4, 131.7, 131.3, 129.7, 127.7. IR, ν (KBr disc): 3400–3200, 3100–2910, 2210, 1670, 1600, 1590, 1240, 1110 cm^{-1}.

6a: ^{1}HNMR δ (DMSO d6): 1.52 (t, 3H, Me), 4.55 (q, 2H, OCH2), 7–7.8 (m, 3H, aromatic protons), 8.68 (s, 1H, olefinic CH), OH is unobserved; IR, ν (KBr disc): 3300–3100, 1725, 1685 cm^{-1}.

6b: ^{1}HNMR δ (DMSO d6): 3.8 (s, 3H, OMe), 6.9-7.7 (m, 3H, aromatic protons), 6.69 (s, 1H, olefinic CH), OH is unobserved, IR, ν (KBr disc): 3290–3090, 1715, 1680 cm^{-1}.

6c: ^{1}HNMR δ (DMSO d6): 6.9–7.9 (m, 3H, aromatic protons), 8.81(s, 1H, olefinic CH), OH is unobserved, IR, ν (KBr disc): 3260–3080 2230, 1685 cm^{-1}.

6d: ^{1}HNMR δ (CDCl3): 2.85 (s, 3H, Me), 7.3–7.85 (m, 4H, aromatic protons), 8.62 (s, 1H, olefinic CH), IR, ν (KBr disc): 1750, 1680 cm^{-1}.

6e: ^{1}HNMR δ (CDCl3): 1.52(t, 3H, Me), 4.55 (q, 2H, OCH2), 7.4–7.9 (m, 4H, aromatic protons), 8.62 (s, 1H, olefinic CH); IR, ν (KBr disc): 1790, 1650 cm^{-1}.

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