

Coumarin Synthesis via Knoevenagel Condensation Reaction in 1,1,3,3-N,N,N',N'-Tetramethylguanidinium Trifluoroacetate Ionic Liquid

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Coumarin derivatives were synthesized in relatively high yields via Knoevenagel condensation reaction of an *ortho*-hydroxyaryl aldehyde and an activated β -dicarbonyl C-H acid in the presence of a recyclable ionic liquid 1,1,3,3-N,N,N',N'-tetramethylguanidinium trifluoroacetate under either classical heating conditions or using microwave irradiation. Application of microwave irradiation decreased the required time by a factor of about 200. The ionic liquid could be recycled several times without loss of efficiency with regards to the reaction times and yields.

Keywords: Coumarin, Microwave irradiation, β -Dicarbonyl C-H acid, Ionic liquid

INTRODUCTION

Coumarins and their derivatives are used in the fields of biology, medicine and polymer science. They are also present or used in perfumes and cosmetics [1-5], cigarettes [2-5], alcoholic beverages [6] and laser dyes [7]. Coumarins have been found to be connected with a number of cases of homicide and suicide in Korea [8].

Coumarins were first synthesized via the Perkin reaction in 1868, and many simple coumarins are still prepared through this method. In the early 1900s, the Knoevenagel reaction emerged as an important synthetic method to synthesize coumarin derivatives with carboxylic acid at the 3-position [9,10]. To date, many other synthetic methods for coumarins have been reported, including the Pechmann [11], Reformatsky [12] and Wittig reactions [13,14].

Coumarin derivatives are readily synthesized by the above-mentioned reactions; however, they usually require harsh reaction conditions and non-environmentally friendly solvents. Recently some good methods for synthesis of coumarin have

been reported [15-17].

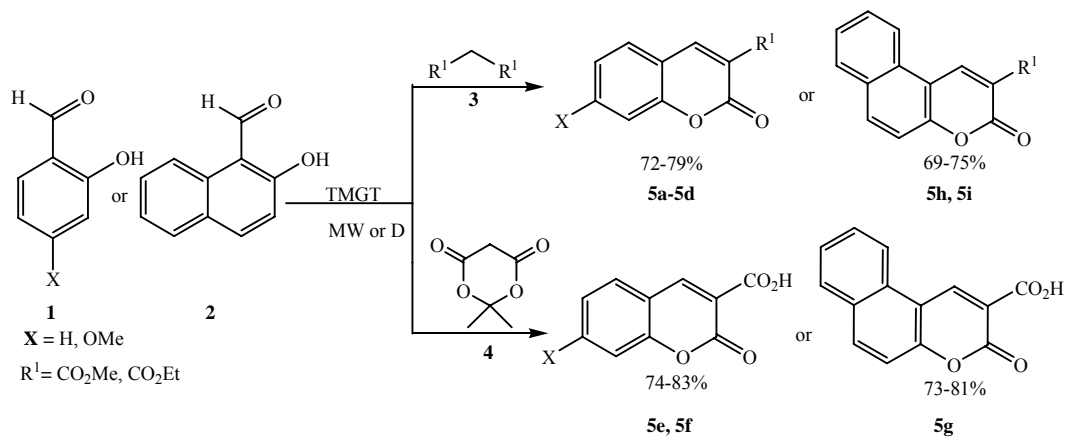
For instance, ionic liquids have attracted extensive interest as environmentally benign reagent to their favorable properties, and a variety of catalytic reactions have been successfully conducted using ionic liquids as solvents [18-20].

In our previous works we have reported our findings on using ionic liquid as a catalyst and solvent in organic transformations [21-26], and synthesis of coumarins [27,28]. In the present article, we wish to modify the Knoevenagel reaction, using 1,1,3,3-N,N,N',N'-tetramethylguanidinium trifluoroacetate (TMGT) as promoter [29], to the synthesis of coumarin-3-carboxylic acids **5e-5g** or their ester derivatives **5a-5d**, **5h** and **5i** by the condensation of an *ortho*-hydroxyaryl aldehyde such as salicylaldehyde **1** or 2-hydroxy-1-naphthaldehyde **2** with an activated β -dicarbonyl C-H acids such as dialkyl malonate **3** or Meldrum's acid **4** under classical heating conditions or using microwave irradiation (Scheme 1).

EXPERIMENTAL

Melting points were measured on an Electrothermal 9100 apparatus. Mass spectra were recorded on a FINNIGAN-

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Scheme 1

MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a BRUKER DRX-300.13 AVANCE spectrometer at 75.47 MHz, respectively. NMR spectra were obtained in CDCl_3 . All the products were new compounds (except **5g** and **5h**) which were characterized by IR, ^1H NMR, ^{13}C NMR and Mass spectral data. The microwave oven was a National model NN-6653 (max. 900 W) with five select power levels one of which was used for this experiment high 100% Wattage.

Typical Procedure for Synthesis of 2H-1-Benzopyran-3-carboxylic Acid, 2-Oxo-methyl Ester (**5a**, $\text{C}_{11}\text{H}_8\text{O}_4$)

Salicylaldehyde (0.425 ml, 3 mmol) and diethyl malonic acid (0.280 ml, 3 mmol) was added to TMGT (0.04 g, 0.2 mmol) in screw capped vial. The reaction mixture was heated with stirring at 120 °C for 30 min or irradiation in microwave oven for 1.5 min. After cooling, the reaction mixture was washed with distilled water (10 ml). As TMGT was soluble in water, pure TMGT was obtained after drying the aqueous layer, which could be reused. The solid residue was dried and crystallized from ethyl acetate: n-hexane (40:60; 10 ml) to yield the product **5a** yield 76%, under classical heating conditions and 79%, under classical MW irradiation, white crystalline, melting point (m.p.): 117-118 °C. IR (KBr): $\nu = 1741, 1694, 1610, 1558, 1241, 1209 \text{ cm}^{-1}$. ^1H NMR (300.13 MHz, CDCl_3 , Me_4Si): δ (ppm): 3.98 (3H, s, CH_3), 7.33-7.70 (4H, m, aroma), 8.59 (1H, s, $\text{C}=\text{CH}$). ^{13}C NMR (300.13 MHz, CDCl_3 , Me_4Si): δ (ppm): 191.39, 154.44, 125.87, 146.93,

132.20, 127.26, 122.60, 115.52, 115.50, 114.48, 50.63. MS (EI, 70 eV): m/z (%) = 204 (24) [M^+], 173 (100), 146 (60), 118 (12), 89 (64), 63 (68), 39 (50).

2H-1-Benzopyran-3-carboxylic acid, 7-methoxy-2-oxo-methyl ester (5b, $\text{C}_{12}\text{H}_{10}\text{O}_5$). Yield: 74%, classical heating conditions and 78%, MW irradiation, orange crystalline, m.p.: 201-203 °C. IR (KBr): $\nu = 1736, 1727, 1695, 1596, 1257, 1212 \text{ cm}^{-1}$. ^1H NMR (300.13.13 MHz, CDCl_3 , Me_4Si): δ (ppm): 3.86 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 6.77-7.48 (3H, m, aroma), 8.50 (1H, s, $\text{C}=\text{CH}$). ^{13}C NMR (300.13 MHz, CDCl_3 , Me_4Si): δ (ppm): 162.71, 154.19, 148.23, 133.50, 129.79, 128.56, 116.86, 116.82, 115.80, 99.31, 67.11, 51.95. MS (EI, 70 eV) m/z (%): 234 (42) [M^+], 203 (100), 173 (22), 149 (24), 119 (32), 89 (16), 20 (40), 43 (20).

2H-1-Benzopyran-3-carboxylic acid, 2-oxo-ethyl ester (5c, $\text{C}_{12}\text{H}_{10}\text{O}_4$). Yield: 74%, classical heating conditions and 75%, MW irradiation, white crystalline, m.p.: 90-91 °C. IR (KBr): $\nu = 1762, 1602, 1591, 1240, 1201 \text{ cm}^{-1}$. ^1H NMR (300.13 MHz, CDCl_3 , Me_4Si): δ (ppm): 1.36 (3H, t, $J = 7.14 \text{ Hz}$, CH_3), 4.37 (2H, q, $J = 7.14 \text{ Hz}$, CH_2), 7.26-7.63 (3H, m, aroma), 8.48 (1H, s, $\text{C}=\text{CH}$). ^{13}C NMR (300.13 MHz, CDCl_3 , Me_4Si): δ (ppm): 163.10, 156.78, 155.18, 148.68, 134.37, 129.51, 124.86, 118.31, 117.89, 116.83, 62.04, 14.26. MS (EI, 70 eV) m/z (%): 219 (40) [M^+], 173 (100), 146 (48), 118 (28), 89 (40), 63 (16), 39 (12).

2H-1-Benzopyran-3-carboxylic acid, 7-methoxy-2-oxo-ethyl ester (5d, $\text{C}_{13}\text{H}_{12}\text{O}_5$). Yield: 72% and classical heating conditions, 75%, MW irradiation, orange crystalline, m.p.: 125-126 °C. IR (KBr): $\nu = 3490, 3037, 3025, 1747, 1604, 1615, 1498, 1210 \text{ cm}^{-1}$. ^1H NMR (300.13 MHz, CDCl_3 ,

Me₄Si): δ (ppm): 1.35 (3H, t, $J = 7.08$ Hz, CH₂), 4.35 (2H, q, $J = 7.08$ Hz, CH₂), 8.46 (1H, s, C=CH). ¹³C NMR (300.13 MHz, CDCl₃, Me₄Si): δ (ppm): 165.68, 163.94, 158.06, 157.74, 149.58, 131.28, 114.50, 114.22, 112.13, 100.86, 62.24, 56.56, 14.82. MS (EI, 70eV) m/z (%): 248 (48) [M⁺], 203 (100), 176 (76), 148 (32), 119 (28), 76 (16), 50 (12).

2H-Naphto[2,1-b]pyran-3-carboxylic acid, 2-oxo (5g, C₁₄H₈O₄). Yield: 73%, classical heating conditions and 81% MW irradiation, yellow crystalline, m.p.: 216-218 °C. IR (KBr): $\nu = 3500, 1731, 1670, 1591, 1566, 1282, 1210$ cm⁻¹. ¹H NMR (300.13 MHz, CDCl₃, Me₄Si): δ (ppm): 7.52-8.40 (6H, m, aroma), 9.65 (1H, s, C=CH). ¹³C NMR (300.13 MHz, CDCl₃, Me₄Si): δ (ppm): 153.20, 156.99, 156.11, 145.22, 136.40, 130.24, 129.45, 129.30, 126.63, 121.53, 116.69, 116.02, 112.35. MS (EI, 70 eV) m/z (%): 240 (64) [M⁺], 212 (20), 196 (54), 198 (82), 139 (100), 118 (34), 89 (30), 63 (32), 39 (20).

2H-Naphto[2,1-b]pyran-3-carboxylic acid, 2-oxo-methyl ester (5h, C₁₅H₁₀O₄). Yield: 71%, classical heating conditions and 75% MW irradiation, yellow crystalline, m.p.: 163-165 °C. IR (KBr): $\nu = 1741, 1639, 1562, 1257, 1205$ cm⁻¹. ¹H NMR (300.13 MHz, CDCl₃, Me₄Si): δ (ppm): 3.97 (3H, s, CO₂CH₃), 7.43-8.31 (6H, m, aroma), 9.34 (1H, s, C=CH). ¹³C NMR (300.13 MHz, CDCl₃, Me₄Si): δ (ppm): 164.25, 156.98, 156.18, 145.20, 136.38, 130.23, 129.45, 129.30, 129.22, 126.64, 121.54, 116.68, 116.01, 112.36, 53.06. MS (EI, 70 eV) m/z (%): 254 (46) [M⁺], 223 (48), 195 (44), 168 (24), 139 (100), 87 (16), 63 (32), 39 (20).

2H-Naphto[2,1-b]pyran-3-carboxylic acid, 2-oxo-ethyl ester (5i, C₁₆H₁₂O₄). Yield: 69%, classical heating conditions and 70% MW irradiation, yellow crystalline, m.p.: 92-93 °C. IR (KBr): $\nu = 1725, 1703, 1563, 1283, 1206$ cm⁻¹. ¹H NMR (300.13 MHz, CDCl₃, Me₄Si): δ (ppm): 1.42 (3H, t, $J = 7.12$ Hz, CH₃), 4.44 (2H, q, $J = 7.13$ Hz, CH₂), 7.41-8.24 (6H, m, aroma), 9.27 (1H, s, C=CH). ¹³C NMR (300.13 MHz, CDCl₃, Me₄Si): δ (ppm): 164.25, 162.71, 155.74, 154.19, 148.23, 133.50, 129.79, 128.56, 127.77, 123.99, 116.86, 115.80, 112.75, 99.31, 51.95, 22.68. MS (EI, 70 eV) m/z (%): 268 (50) [M⁺], 223 (50), 196 (70), 168 (60), 139 (100), 163.

RESULT AND DISCUSSION

As can be seen in Table 1, coumarins were produced in

high yields varying from 69-83% under classical heating conditions or microwave irradiation. The yields of the reactions were comparable to those obtained under heterogeneous conditions when the reaction was carried out in the presence of KSF clay in water at reflux conditions or under solvent free conditions at 160 °C [30]. However, the reaction times were reduced from a day to several minutes or a few hours.

As indicated in Table 1, application of microwave irradiation decreased the required time by a factor of about 200.

It is important to note that no product could be detected when a mixture of salicylaldehyde and dimethyl malonate or Meldrum's acid (mole ratio 1:1) was heated in the absence of ionic liquid at 120 °C for 8 h or using microwave irradiation (3 min), which indicated the necessity for application of ionic liquid for this reaction.

Another advantage of the ionic liquid is its ability to be recycled as a reaction medium. We were able to easily separate TMGT from reaction medium by washing it with water and evaporating the solvent under vacuum, and reusing it for the subsequent reactions. As indicated in Table 1 (Entry 5a), there was no loss of efficiency with regards to the reaction times and yields after four times. However, to obtain comparable results, fresh ionic liquid should be used in the reaction.

In summary, a novel method for the synthesis of 3-substituted coumarins by the Knoevenagel condensation of *ortho*-hydroxyaryl aldehyde and dialkyl malonate or Meldrum's acid using TMGT as a promoter under classical heating conditions or using microwave irradiation under solvent-free conditions was developed in good yields.

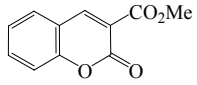
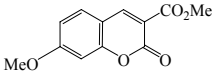
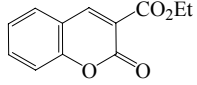
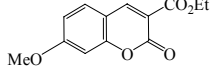
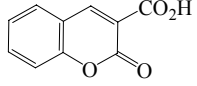
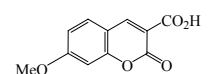
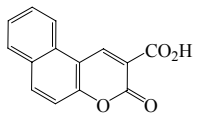
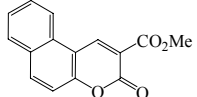
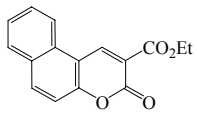
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Table 1. Synthesis of Coumarin *via* Knoevenagel Condensation of an *ortho*-hydroxyaryl Aldehyde with an Activated β -Dicarbonyl C-H Acid under Classical Heating Conditions or Using Microwave Irradiation in TMGT

Entry	R ¹	Product	T = 120 °C Yields (%)/ Time (min)	MW Yields (%)/ Time (min)	MP (°C) Found (Reported)
5a	CO ₂ Me		76/30 75, 62, 58 ^a	79/1.5, 79, 74, 61 ^a	117-118
5b	CO ₂ Me		74/60	78/2	201-203
5c	CO ₂ Et		74/120	75/2	90-91
5d	CO ₂ Et		72/210	75/3	125-126
5e	Meldrum's acid		78/120 ^b	83/1	190-192 (191-192) ^c
5f	Meldrum's acid		74/150 ^b	80/1	193-195 (192-194) ^c
5g	Meldrum's acid		73/240 ^b	81/2	216-218
5h	CO ₂ Me		71/150	75/3	163-165
5i	CO ₂ Et		69/480	70(4)	92-93

^aThe same ionic liquid was used for each of the three runs. ^bThe reaction is carried out at 80 °C. ^cRef [31].

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