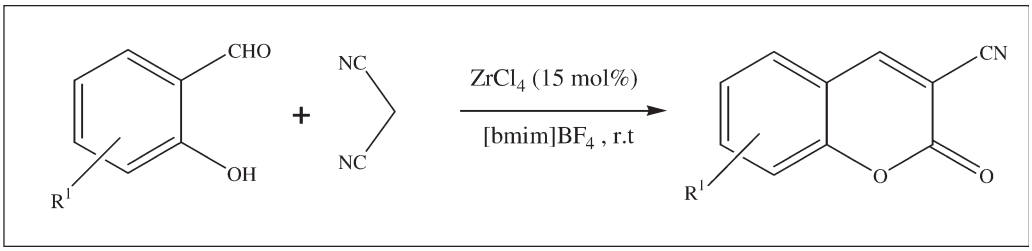
$ZrCl_4$/[bmim]BF_4-Catalyzed Condensation of Salicylaldehydes and Malononitrile: Single-Step Synthesis of 3-Cyanocoumarin Derivatives

Hassan Valizadeh,* Manzar Mahmoodian, and Hamid Gholipour

Department of Chemistry, Faculty of Sciences, Azarbaijan University of Tarbiat Moallem, Tabriz, Iran
*E-mail: h-valizadeh@azaruniv.edu

Received February 3, 2010
DOI 10.1002/jhet.593
Published online 11 April 2011 in Wiley Online Library (wileyonlinelibrary.com).



A versatile and efficient single-step route to 3-cyanocoumarins *via* Knoevenagel condensation of salicylaldehydes and malononitrile using $ZrCl_4$ as the catalyst (15 mol %) in ionic liquid 1-(*n*-butyl)-3-methylimidazolium tetrafluoroborate as reaction medium and catalyst is described. The novel procedure features single step, short reaction time, good yields, and simple workup.

J. Heterocyclic Chem., **48**, 799 (2011).

INTRODUCTION

Coumarins and their derivatives are very important organic compounds. They are the structural unit of several natural products [1]. Their applications range from pharmaceuticals [2], optical brighteners [3], and laser dyes [4]. Also, coumarins and functionalized coumarins have shown activity as antimicrobials and chemotherapeutics [5]. These properties have made coumarins interesting targets for organic chemists. Coumarins have been synthesized using several synthetic routes such as Pechmann, Perkin, Knoevenagel, Reformatsky, and Wittig reactions. However, due to simple and relatively inexpensive starting materials, the Knoevenagel reaction was widely used for the synthesis of coumarins.

Knoevenagel condensation is one of the most important methods for carbon–carbon double bond formation in synthetic chemistry [6]. Generally, Knoevenagel reactions are carried out by the condensation of active methylene compounds with aldehydes, with some organic bases, as well as their salts as catalysts. Alternative protocols for Knoevenagel condensations catalyzed by Lewis acids and various heterogeneous solid bases have been reported in literature [7–9]. We reported the synthesis of coumarin derivatives *via* Knoevenagel reaction of 2-hydroxybenzaldehyde derivatives with some active methylene compounds in aqueous media and also in ionic liquids [10,11].

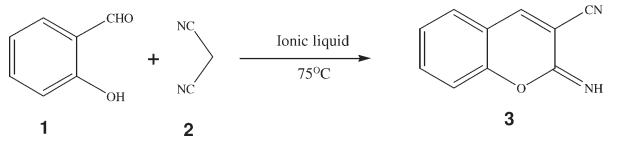
Several publications report the preparation of 2-iminochromene from Knoevenagel condensation of 1:1 mixture of the salicylaldehydes and malononitrile [12]. Proença and coworkers [13] reported the synthesis of new dimeric chromene derivatives *via* Knoevenagel condensation of malononitrile and salicylaldehydes by a delicate control of the experimental conditions. Yamashita *et al*. [14] synthesized of 3-cyanocoumarins from Ti(O-i-Pr)$_4$-catalyzed Knoevenagel condensation of malononitrile and salicylaldehydes in isopropyl alcohol as a solvent. Recently, we reported the synthesis of benzo[b]-pyran-2-imines *via* Knoevenagel condensation of malononitrile and salicylaldehydes over MgO and subsequent transformation to the coumarins derivatives by hydrolysis under acidic conditions [15]. In continuation of our work [16] on the development of efficient and environmentally benign procedures in synthetic organic chemistry, we wish to report the synthesis of 3-cyanocoumarins from single-step $ZrCl_4$/[bmim]BF_4-catalyzed Knoevenagel reaction of salicylaldehydes and malononitrile at room temperature.

RESULTS AND DISCUSSION

A typical reaction of salicylaldehyde and malononitrile was carried out in the ionic liquid, [bmim]Cl, at ambient conditions to form benzo[b]pyran-2-imine **3** (Scheme 1).

At room temperature, the reaction did not proceed further to afford the product. So, it was carried out at higher temperatures and the optimum results were obtained at

Scheme 1



75°C (32%). For further optimization, several ionic liquids (ILs) based on butylmethylimidazolium salts, [bmim]X, with varying anions were screened for the above typical reaction at 75°C. Evidently, 1-(*n*-butyl)-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) was found to be superior in terms of yield (42%) and reaction time (2 h) when compared with other ILs (Table 1).

An experiment to demonstrate the catalytic ability of $ZrCl_4$ was carried out in [bmim]BF_4 for this procedure. In contrast, reactions of the salicylaldehyde and malononitrile do not lead just to benzo[b]pyran-2-imine **3** but also to coumarins **4a** (Scheme 2). In the presence of equimolar amount of $ZrCl_4$, product **4a** was produced in 52% yield for 30 min at room temperature in [bmim]BF_4 (entry 11, Table 1). To find an optimal amount of catalyst for the model reaction, the amount of catalyst was reduced from 100 to 0.1% (molar fraction). The results are collected in Table 1. The reactivity for the lower amount of $ZrCl_4$ (0.1% molar fraction) decreased obviously and two products **3** and **4a** were produced under these conditions. According to the results from Table 1, we choose 15% molar fraction as an optimal amount of catalyst for further experiments. The reaction in the absence of [bmim]BF_4 was so sluggish that afforded the low yield of the unidentified mixture of products.

With the best reaction conditions in hand, we investigated the reaction of various salicylaldehyde derivatives with malononitrile. Salicylaldehydes containing different substituents were reacted efficiently and afforded good yields of coumarins **4a–i** under these conditions (Scheme 2).

CONCLUSIONS

In summary, we have developed a single step, convenient, and efficient synthetic approach to synthesize 3-cyanocoumarins *via* the $ZrCl_4$/[bmim]BF_4-catalyzed Knoevenagel condensation of malononitrile with salicylaldehyde derivatives at room temperature. Because of the short reaction times with good yields and simple work up procedure, this methodology could serve as a valuable alternative to known methods.

EXPERIMENTAL

General information. All reagents were purchased from Merck Company and used without further purification. Infrared spectra were recorded in KBr and were determined on a Perkin Elmer FTIR spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Avance AC-400 MHz using DMSO-d_6 as the deuterated solvents and tetramethylsilane (TMS) as internal standard. All melting points are uncorrected and measured in open glass capillaries using Stuart melting point apparatus. Elemental analyses were carried out on a Perkin-Elmer 240C elemental analyzer and are reported in percent atomic abundance.

General procedure for the synthesis of 3-cyanocoumarins (4a–i). Salicylaldehyde derivative (15 mmol) and malononitrile (15 mmol) were added to [bmim]BF_4 (3 mL) and mixed thoroughly for 10 min. $ZrCl_4$ (15 mol %) was added to the mixture and stirred at room temperature. After completion of the reaction, as indicated by thin layar chromotography (TLC; ethylacetate/*n*-hexane, 2/5), the mixture was extracted with ethylacetate. The extracts were concentrated on a rotary evaporator and the crude mixture was purified by recrystallization from ethanol/water to give pure coumarins (**4a–i**).

3-Cyano benzo[b]pyran-2-imine (3). White solid; mp: 141–143°C (lit. [14] 140–141°C); IR (KBr) (ν_{max}/cm^{-1}): 3310,

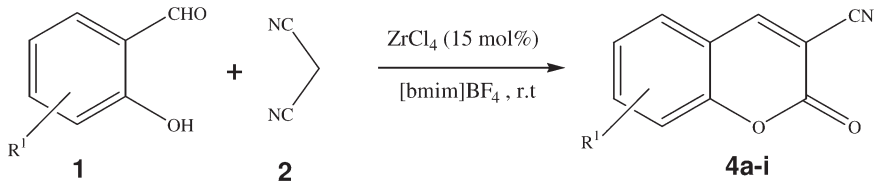
Table 1

Knoevenagel condensation of salicylaldehyde and malononitrile under different conditions[a]

Entry	Ionic liquid	$ZrCl_4$ (mol %)	Temperature (°C)	Time (min)	Product	Yield[c] (%)
1	[bmim]Cl	0	0	180	**3**	<20
2	[bmim]Cl	0	75	120	**3**	32
3	[bmim]Br	0	75	120	**3**	38
4	[bmim]BF_4	0	75	120	**3**	42
5	[bmim]BF_4	0.1	25	40	**3:4a** (35:20)[b]	55
6	[bmim]BF_4	5	25	40	**3:4a** (20:52)[b]	72
7	[bmim]BF_4	10	25	35	**4a**	73
8	[bmim]BF_4	15	25	35	**4a**	83
9	[bmim]BF_4	25	25	30	**4a**	75
10	[bmim]BF_4	50	25	30	**4a**	62
11	[bmim]BF_4	100	25	30	**4a**	52

[a] Salicylaldehyde (15 mmol) and malononitrile (15 mmol).
[b] Products **3** and **4a** were produced under these conditions.
[c] Isolated yield of product.

Scheme 2



1 **2** **4a-i**

4a: R^1 = H **4d:** R^1 = 7-OH **4g:** R^1 = 8-OMe
4b: R^1 = 5-OH **4e:** R^1 = 8-OH **4h:** R^1 = 7-NEt_2
4c: R^1 = 6-OH **4f:** R^1 = 7-OMe **4i:** R^1 = 6-Br

2220, 1651; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.46 (m, 2H), 7.49 (dd, J = 8.15, 1.44 Hz, 1H), 7.68 (dd, J = 8.05, 1.43 Hz, 1H), 8.14 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 105.13, 117.08, 117.43, 119.09, 119.91, 127.82, 131.81, 139.12, 150.45, 162.32; Anal. Calcd for $C_{10}H_6N_2O$: C, 70.58; H, 3.55; N, 16.46. Found: C, 71.40; H, 3.58; N, 16.54.

2-Oxo-2H-chromene-3-carbonitrile (4a). White solid; Yield: (83%); mp: 183–185°C (lit. [17] 184–185°C); IR (KBr) (ν_{max}/cm^{-1}): 2220, 1712, 1645; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.44 (m, 2H), 7.65 (dd, J = 7.46, 1.62 Hz, 1H), 7.75 (dd, J = 7.54, 1.45 Hz, 1H), 8.30 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 103.61, 112.00, 117.56, 117.22, 128.15, 128.21, 136.50, 152.11, 155.20, 156.88; Anal. Calcd (%) for $C_{10}H_5NO_2$: C, 70.18; H, 2.94; N, 8.18. Found (%): C, 70.23; H, 2.95; N, 8.21.

5-Hydroxy-2-oxo-2H-chromene-3-carbonitrile (4b). Yellow solid; Yield: (81%); mp: 229–232°C; IR (KBr) (ν_{max}/cm^{-1}): 3383 (broad), 2223, 1719, 1611; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.29 (dd, J = 7.98, 8.11 Hz, 1H), 7.33 (dd, J = 7.98, 1.31 Hz, 1H), 7.60 (dd, J = 8.11, 1.31 Hz, 1H), 8.12 (s, 1H), 8.79 (s, 1H, OH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 109.71, 118.80, 119.08, 121.65, 124.31, 131.32, 136.45, 145.85, 156.63, 164.24; Anal. Calcd for $C_{10}H_5NO_3$: C, 64.18; H, 2.69; N, 7.48. Found: C, 64.29; H, 2.73; N, 7.52.

6-Hydroxy-2-oxo-2H-chromene-3-carbonitrile (4c). Yellow solid; Yield: (80%); mp: 236–239°C (lit. [14] 237–238°C); IR (KBr) (ν_{max}/cm^{-1}): 3391 (broad), 2250, 1710, 1645; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.12 (d, J = 2.01 Hz, 1H), 7.20 (dd, J = 7.68, 2.01 Hz, 1H), 7.35 (d, J = 7.68 Hz, 1H), 8.85 (s, 1H), 8.85 (s, 1H, OH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 102.56, 113.54, 116.23, 117.02, 127.89, 130.23, 138.63, 151.56, 156.54, 158.02; Anal. Calcd (%) for $C_{10}H_5NO_3$: C, 64.18; H, 2.69; N, 7.48. Found (%): C, 64.22; H, 2.71; N, 7.45.

7-Hydroxy-2-oxo-2H-chromene-3-carbonitrile (4d). Yellow solid; Yield: (84%); mp: 246–248°C (lit. [18] 249–251°C); IR (KBr) (ν_{max}/cm^{-1}): 3395 (broad), 2227, 1720, 1638; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.13 (dd, J = 8.85, 2.41 Hz, 1H), 7.15 (d, J = 2.41 Hz, 1H), 7.78 (d, J = 8.85 Hz, 1H), 8.78 (s, 1H), 8.81 (s, 1H, OH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 104.25, 114.45, 117.85, 121.12, 128.05, 133.32, 138.68, 154.58, 159.46, 161.09; Anal. Calcd (%) for $C_{10}H_5NO_3$: C, 64.18; H, 2.69; N, 7.48. Found (%): C, 64.25; H, 2.71; N, 7.51.

8-Hydroxy-2-oxo-2H-chromene-3-carbonitrile (4e). Yellow solid; Yield: (80%); mp: 228–230°C (lit. [14] 228–230°C); IR (KBr) (ν_{max}/cm^{-1}): 3385 (broad), 2253, 1745, 1641; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.21–7.38 (m, 3H), 8.75 (s, 1H), 8.89 (s, 1H, OH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 104.54, 114.41, 115.32, 119.98, 128.02, 131.23, 136.98, 152.24, 157.02, 160.32; Anal. Calcd (%) for $C_{10}H_5NO_3$: C, 64.18; H, 2.69; N, 7.48. Found (%): C, 64.19; H, 1.67; N, 7.47.

7-Methoxy-2-oxo-2H-chromene-3-carbonitrile (4f). Yellow solid; Yield: (83%); mp: 224–226°C (lit. [14] 225–226°C); IR (KBr) (ν_{max}/cm^{-1}): 2227, 1720, 1638; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.90 (s, 3H), 7.11 (dd, J = 8.71, 2.39 Hz, 1H), 7.15 (d, J = 2.39 Hz, 1H), 7.76 (d, J = 8.71 Hz, 1H), 8.85 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 63.71, 105.52, 115.25, 116.63, 120.20, 127.87, 130.36, 137.74, 153.56, 158.36, 159.16; Anal. Calcd (%) for $C_{11}H_7NO_3$: C, 65.67; H, 3.51; N, 6.96. Found (%): C, 65.85; H, 3.56; N, 6.60.

8-Methoxy-2-oxo-2H-chromene-3-carbonitrile (4g). Yellow solid; Yield: (84%); mp: 224–226°C (lit. [17] 225–226°C); IR (KBr) (ν_{max}/cm^{-1}): 2253, 1745, 1641; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.90 (s, 3H), 7.20–7.41 (m, 3H), 8.88 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 67,11, 102.23, 115.56, 116.23, 120.54, 127.89, 132.23, 137.63, 153.63, 158.85, 160.36; Anal. Calcd (%) for $C_{11}H_7NO_3$: C, 65.67; H, 3.51; N, 6.96. Found (%): C, 65.80; H, 3.55; N, 6.71.

7-Diethylamino-2-oxo-2H-chromene-3-carbonitrile (4h). Yellow solid; Yield: (79%); mp: 210–213°C (lit. [14] 211–212°C); IR (KBr) (ν_{max}/cm^{-1}): 2217, 1715, 1640; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.23 (t, J = 6.87 Hz, 6H), 3.45 (q, J = 6.87 Hz, 4H), 6.47 (d, J = 2.3 Hz, 1H), 6.60 (dd, J = 8.89, 2.45 Hz, 1H), 7.31 (d, J = 8.89 Hz, 1H), 7.99 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 15.21, 56.63, 105.52, 115.25, 116.63, 120.20, 127.87, 130.36, 137.74, 153.56, 158.36, 159.16; Anal. Calcd (%) for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. Found (%): C, 69.22; H, 5.84; N, 11.67.

6-Bromo-2-oxo-2H-chromene-3-carbonitrile (4i). White solid; Yield: (88%); mp: 201–202°C (lit. [17] 200–201°C); IR (KBr) (ν_{max}/cm^{-1}): 2223, 1732, 1641; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.15 (d, J = 7.36 Hz, 1H), 7.25 (dd, J = 7.36, 1.96 Hz, 1H), 7.41 (d, J = 1.96 Hz, 1H), 8.82 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 105.52, 114.32, 116.02, 119.98, 128.63, 131.08, 138.78, 152.42, 157.86, 160.32; Anal. Calcd (%) for $C_{10}H_4BrNO_2$: C, 48.03; H, 1.61; N, 5.60. Found (%): C, 48.20; H, 1.64; N, 5.65.

Acknowledgments. The partial financial assistance from the Research Vice Chancellor of Azarbaijan University of Tarbiat Moallem is gratefully acknowledged.

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