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Abstract: A series of 3-acetoacetylcoumarin derivatives were synthesized via the reaction of substituted 2-hydroxybenzaldehydes and 4-hydroxy-6-methyl-2*H*-pyran-2-one in ionic liquid. This method has the advantages of good yields, milder reaction conditions, easier workup, no catalyst, and environmentally benign procedure.

Keywords: 3-Acetoacetylcoumarin, 2-hydroxybenzaldehyde, 4-hydroxy-6-methyl-2*H*-pyran-2-one, ionic liquid

Coumarin and its derivatives are natural compounds and are important chemicals in perfume, cosmetic, and pharmaceutical industrial production.[1] Some coumarin derivatives have been reported to exhibit biological properties, such as anti-oxidant, anti-inflammatory, antiallergic, hepatoprotective, antiviral, anticarcinogenic, and anticoagulant properties.[2–10] They have attracted considerable interest in recent years because of these diverse pharmacological properties.[11] 3-Acetoacetylcoumarin derivatives are generally prepared by the reaction of 2-hydroxybenzaldehydes and 4-hydroxy-6-methyl-2*H*-pyran-2-one in an

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organic solvent (e.g., ethanol or toluene) in the presence of a base like triethylamine[12] and potassium fluoride (KF)–alumina[13] or catalyzed by ammonium acetate.[14]

Room-temperature ionic liquids, especially those based on 1-alkyl-3-methylimidazolium cations, have shown great promise as an attractive alterative to conventional organic solvents, and more attention has been currently focused on organic reactions promoted by ionic liquids.[15] They are nonvolatile, recyclable, nonexplosive, easily operable, and thermally robust.[16] There are many reports concerning the applications of ionic liquids in organic reactions, such as Friedel–Crafts reactions,[17] Diels–Alder reactions,[18] Heck reactions,[19] Pechmann condensations,[20] Biginelli reactions,[21] Beckmann rearrangements,[22] and other reactions.[23] As part of our current studies on the development of new routes to heterocyclic system in ionic liquids,[24] we now report an efficient and clean synthetic route to 3-acetoacetylcoumarin derivatives in ionic liquid [bmim]Br.

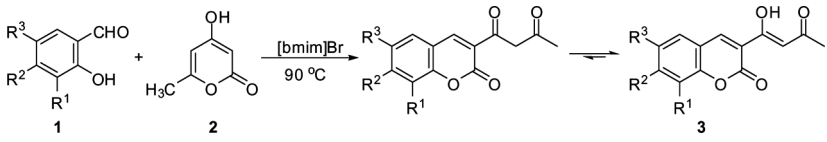
To get 3-acetoacetylcoumarin derivatives **3**, we reported a facile method consisting of substituted 2-hydroxybenzaldehyde **1** and 4-hydroxy-6-methyl-2*H*-pyran-2-one **2** in an ionic liquid [bmim]Br at 90°C for a few hours (Scheme 1).

It is well-known that choosing an appropriate solvent and reaction temperature is crucially important for an efficient organic synthesis. To search for the optimal reaction conditions, the reaction of salicylaldehyde **1a** and 4-hydroxy-6-methyl-2*H*-pyran-2-one **2** was examined using different solvents and different reaction temperatures. The corresponding results are summarized in Table 1.

It is shown in Table 1 that the ionic liquid [bmim]Br as solvent at 90°C resulted in the best yield and shortest reaction time. Therefore, [bmim]Br was chosen as the solvent for this reaction.

Under these optimized reaction conditions, a series of 3-acetoacetylcoumarin derivatives **3** were synthesized. The results are summarized in Table 2.

The structure of **3a** was based on the spectroscopic data and high-resolution mass spectra (HRMS). It should be noted that the infrared (IR) spectra exhibited broad bands at 3441 cm^{-1} (OH) and



Scheme 1. The synthetic route for the 3-acetoacetylcoumarin derivatives **3**.

Table 1. Solvent and reaction temperature optimization for the synthesis of **3a**

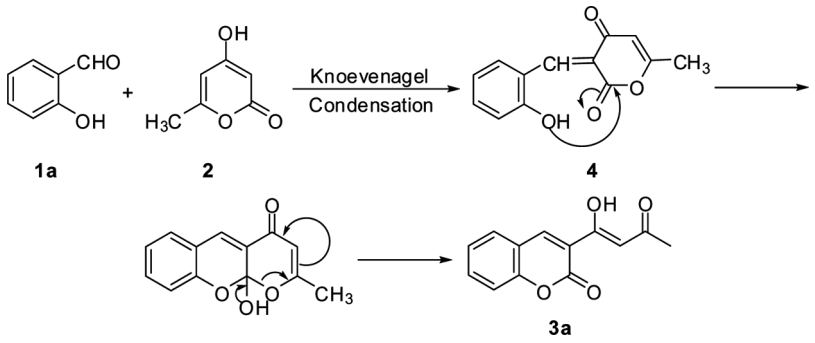
Entry	Solvent	Reaction temperature (°C)	Time (h)	Yield (%)
1	[bmim]Br	90	4	98
2	[bmim]BF_4	90	8	54
3	[bmim]PF_6	90	8	60
4	[bmim]Br	Rt	30	56
5	[bmim]Br	40	21	65
6	[bmim]Br	60	12	73
7	[bmim]Br	80	8	85
8	CH_3COCH_3	Reflux	29	28
9	CH_3CN	Reflux	25	33
10	EtOH	Reflux	18	71
11	$CHCl_3$	Reflux	30	23
12	DMF	100	7	81

1730 cm^{-1} (C=O), and the NMR spectra (in solvent $CDCl_3$) showed the absence of the methylene (CH_2) group and instead a singlet at 15.80 ppm (OH) and a singlet at 6.97 ppm (CH). We can see clearly that it was an enol form, not a keto tautomerism, perhaps the large-conjugative-system-stable enol moiety. The structures are the same as in our previous results.[13]

On the basis of the structure of **3**, the following mechanistic pathway leading to the parent heterocycle **3a** can be formulated. It starts with the Knoevenagel condensation of pyranone **2** with salicylaldehyde (**1a**) in ionic liquid to give 3-salicylidenepyrane-2,4-dione **4**. This compound

Table 2. Synthesis of 3-acetoacetylcoumarin derivatives **3** in [bmim]Br at 90°C

Entry	Product	R^1	R^2	R^3	Time (h)	Yield (%)
1	**3a**	H	H	H	4	98
2	**3b**	Br	H	Br	4	99
3	**3c**	H	H	Cl	4.5	85
4	**3d**	H	H	Br	4	92
5	**3e**	Cl	H	Cl	3	90
6	**3f**	CH_3O	H	H	4	88
7	**3g**	$(CH_3)_3C$	H	$(CH_3)_3C$	3	56
8	**3h**	H	CH_3O	H	3	80
9	**3i**	H	H	CH_3O	2.5	93
10	**3j**	H	H	CH_3	3	86



Scheme 2. The mechanistic pathway leading to the 3-acetoacetylcoumarin.

was already described as produced from the same components and sodium amide in liquid ammonia.[25] The functional pyrone unit in **4** undergoes a ring-opening reaction mediated by a nucleophic attack of the phenolic group onto the lactone carbonyl, yielding 3-acetoacetylcoumarin (**3a**). A plausible mechanism for the formation of **3a** is outlined in Scheme 2.

In conclusion, with good yields and mild conditions, we think that the present work provides a useful method for the preparation of 3-acetoacetylcoumarin derivatives. Compared with other methods, this new method has the advantages of easier workup, milder reaction conditions, better yields, no catalyst, and a more environmentally benign procedure.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a Tensor 27 spectrometer in KBr with absorptions in centimeters^{-1}. ^{1}H NMR was measured on an Inova 400-MHz spectrometer in $CDCl_3$ with tetramethylsilane (TMS) as internal standard. High-resolution mass spectra (HRMS) were obtained using a time-of-flight mass spectrometry (TOF-MS) instrument.

General Procedure for the Preparation of 3-Acetoacetylcoumarin Derivatives (3)

A dry 50 mL flask was charged with substituted 2-hydroxybenzaldehyde **1** (1 mmol), 4-hydroxy-6-methyl-2*H*-pyran-2-one **2** (1 mmol), and **2 mL** [Bmim]Br. The mixture was stirred at 90°C for 2.5–4.5 h, and the sticky

liquor was poured into water. Then solid material was filtered off and washed with water, and the crude product was purified by recrystallization from ethanol to give pure **3**.

SPECTRAL DATA

3-Acetoacetylcoumarin (3a)

Mp: 144–145 °C (lit.[14] 148–150°C); IR (KBr) *v*: 3441, 3131, 3063, 1730, 1608, 1585, 1455, 1362, 1262, 1301, 1186, 1108, 820, 761 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.24 (3H, s, CH_3), 6.97 (1H, s, CH), 7.25–7.32 (2H, m, ArH), 7.54–7.59 (2H, m, ArH), 8.59 (1H, s, CH), 15.80 (1H, s, OH). HRMS calcd. for $C_{13}H_{10}O_4$, *m/z*: 230.0579 (M^+); found, *m/z*: 230.0580.

6,8-Dibromo-3-acetoacetylcoumarin (3b)

Mp: 186–187°C (lit.[13] 188–189°C); IR (KBr) *v*: 3457, 3121, 3065, 1757, 1619, 1575, 1450, 1363, 1208, 1187, 864, 826, 772 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.23 (3H, s, CH_3), 6.93 (1H, s, CH), 7.66 (1H, d, $J = 2.0$ Hz, ArH), 7.90 (1H, d, $J = 2.0$ Hz, ArH), 8.45 (1H, s, CH), 15.67 (1H, s, OH). HRMS calcd. for $C_{13}H_8{}^{79}Br_2O_4$, *m/z*: 385.8789 (M^+); found, *m/z*: 385.8787.

6-Chloro-3-acetoacetylcoumarin (3c)

Mp: 197–198°C (lit.[13] 197–199°C); IR (KBr) *v*: 3437, 3064, 1737, 1613, 1578, 1480 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.24 (3H, s, CH_3), 7.01 (1H, s, CH), 7.32 (1H, d, $J = 8.88$, ArH), 7.56–7.59 (1H, m, ArH), 7.62 (1H, d, $J = 2.0$, ArH), 8.57 (1H, s, CH), 15.78 (1H, s, OH). HRMS calcd. for $C_{13}H_9{}^{37}ClO_4$, *m/z*: 266.0160 (M^+); found, *m/z*: 266.0165.

6-Bromo-3-acetoacetylcoumarin (3d)

Mp: 209–211°C (lit.[13] 211–212°C); IR (KBr) *v*: 3437, 3064, 1736, 1611, 1583, 1551, 1403, 1280, 1257, 1184, 1110, 1017, 885, 822, 781 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.25 (3H, s, CH_3), 6.97 (1H, s, CH), 7.23 (1H, d, $J = 8.8$ Hz, ArH), 7.68 (1H, dd, $J_1 = 8.8$ Hz, $J_2 = 2.4$ Hz, ArH), 7.74

(1H, d, $J = 2.4$ Hz, ArH), 8.53 (1H, s, CH), 15.75 (1H, s, OH). HRMS calcd. for $C_{13}H_9{}^{79}BrO_4$, m/z: 307.9684 (M^+); found, m/z: 307.9693.

6,8-Dichloro-3-acetoacetylcoumarin (3e)

Mp: 198–200°C (lit.[13] 200–202°C); IR (KBr) ν: 3457, 3116, 3066, 1747, 1614, 1576, 1417, 1365, 1274, 1225, 1183, 1097, 1011, 886, 830, 777, 736, 704 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.25 (3H, s, CH_3), 6.69 (1H, s, CH), 7.50 (1H, s, ArH), 7.62 (1H, s, ArH), 8.50 (1H, s, CH), 15.70 (1H, s, OH). HRMS calcd. for $C_{13}H_8{}^{35}Cl_2O_4$, m/z: 297.9800 (M^+); found, m/z: 297.9791.

8-Methoxy-3-acetoacetylcoumarin (3f)

Mp: 170–172°C (lit.[14] 172–173°C); IR (KBr) ν: 3446, 2941, 2844, 1725, 1605, 1575, 1474, 1441, 1278, 1185, 1124, 1098, 820, 789, 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.21 (3H, s, CH_3), 3.93 (3H, s, OCH_3), 6.99 (1H, s, CH), 7.12–7.17 (2H, m, ArH), 7.20–7.25 (1H, m, ArH), 8.58 (1H, s, CH), 15.79 (1H, s, OH). HRMS calcd. for $C_{14}H_{12}O_5$, m/z: 260.0685 (M^+); found, m/z: 260.0695.

6,8-Di-*tert*-butyl-3-acetoacetylcoumarin (3g)

Mp: 163–165°C. IR (KBr) ν: 3444, 3123, 3070, 1724, 1619, 1581, 1441, 1396, 1363, 1332, 1283, 1252, 1188, 1107, 1012, 893, 835, 792, 711 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.31 [9H, s, $(CH_3)_3C$], 1.47 [9H, s, $(CH_3)_3C$], 2.22 (3H, s, CH_3), 6.99 (1H, s, CH), 7.39 (1H, d, $J = 2.0$ Hz, ArH), 7.62 (1H, d, $J = 2.0$ Hz, ArH), 8.59 (1H, s, CH), 15.83 (1H, s, OH). HRMS calcd. for $C_{21}H_{26}O_4$, m/z: 342.1831 (M^+); found, m/z: 342.1831.

7-Methoxy-3-acetoacetylcoumarin (3h)

Mp: 176–177°C (lit.[13] 175–177°C); IR (KBr) ν: 3447, 2937, 1728, 1609, 1506, 1558, 1426, 1362, 1274, 1224, 1181, 1122, 1022, 843, 810, 772 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.18 (3H, s, CH_3), 3.83 (3H, s, OCH_3), 6.76 (1H, d, $J = 2.4$ Hz, ArH), 6.83 (1H, dd, $J_1 = 8.8$ Hz, $J_2 = 2.4$ Hz, ArH), 6.91 (1H, s, CH), 7.46 (1H, d, $J = 8.8$ Hz, ArH), 8.53 (1H, s, CH), 15.92 (1H, s, OH). HRMS calcd. for $C_{14}H_{12}O_5$, m/z: 260.0685 (M^+); found, m/z: 260.0694.

6-Methoxy-3-acetoacetylcoumarin (3i)

Mp: 170–171°C; IR (KBr) *v*: 3446, 3123, 1732, 1603, 1567, 1494, 1456, 1419, 1361, 1293, 1269, 1184, 1108, 1031, 959, 856, 827, 808 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.24 (3H, s, CH_3), 3.84 (3H, s, OCH_3), 7.01 (2H, s, CH + ArH), 7.19 (1H, dd, $J_1 = 8.8$ Hz, $J_2 = 2.4$ Hz, ArH), 7.27 (1H, d, $J = 8.8$ Hz, ArH), 8.58 (1H, s, CH), 15.82 (1H, s, OH). HRMS calcd. for $C_{14}H_{12}O_5$, *m/z*: 260.0685 (M^+); found, *m/z*: 260.0695.

6-Methyl-3-acetoacetylcoumarin (3j)

Mp: 176–178°C (lit.[13] 179–180°C); IR (KBr) *v*: 3441, 2925, 1733, 1615, 1570, 1489, 1419, 1293, 1261, 1221, 1180, 1137, 1014, 957, 809 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.21 (3H, s, CH_3), 2.37 (3H, s, CH_3), 7.03 (1H, s, CH), 7.26–7.28 (1H, m, ArH), 7.43–7.47 (2H, m, ArH), 8.61 (1H, s, CH), 15.83 (1H, s, OH). HRMS calcd. for $C_{14}H_{12}O_4$, *m/z*: 244.0736 (M^+); found, *m/z*: 244.0746.

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