Synthesis of furan annulated heterocycles via a one-pot three-component reaction

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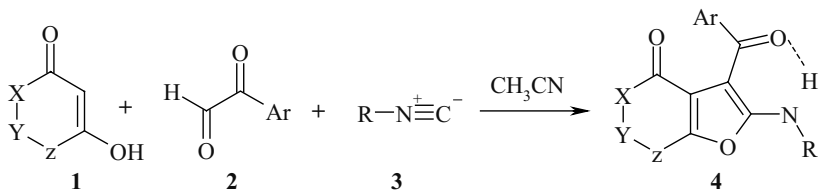
Three-component reaction between 4-hydroxycoumarin, or 5,5-dimethyl-1,3-cyclohexandione, arylglyoxals, and alkyl isocyanides in acetonitrile afforded furocoumarin or benzofuran derivatives in high yields.

Keywords: isocyanide, furocoumarin, multi-component reaction, arylglyoxals, 4-hydroxycoumarin

Furocoumarins and benzofurans are an important class of heterocyclic compounds possessing anticoagulant, insecticide, anthelminthic, hypnotic, antifungal, and HIV protease inhibition activity.[1-5] They are inherently photosensitive and found to have therapeutic uses. The photochemotherapeutic effect relies on their ability to intercalate with the pyrimidine bases of microorganism DNA.[6] Although there are several methods available for the synthesis of furocoumarins[7-10] their application has been limited by difficulties in controlling the regiochemistry of the linear and angular adduct.[7,8] Some multi-step reactions[9,10] have been utilised for the synthesis of furocumarin derivatives. These methods usually suffer from drawbacks such as long reaction times, high temperature and harsh reaction conditions, which cause decreasing of regiochemistry of the reaction. Multi-component reactions (MCRs), because of their productivity, simple procedures, convergence, and facile execution, are one of the best tools in combinatorial chemistry.[11] A three-component reaction between 4-hydroxycoumarin, aromatic aldehydes, and cyclohexyl isocyanide in benzene under reflux conditions has been recently reported for the synthesis of furocoumarin derivatives.[12] Continuing our interest in isocyanide-based multicomponent reactions[13-16] here we describe an efficient synthesis of 2-alkylamino-3-(aryl)-furo[3,2-c]chromen-4-ones or 3-(aryl)-2-alkylamino-6,6-dimethyl-6,7-dihydro-5H-benzofuran-4-one **4** via the one-pot reaction of 4-hydroxycoumarin or, 5,5-dimethyl-1,3-cyclohexandione (**1**) with an arylglyoxal **2** and an isocyanide **3** in high yields without using any catalyst (Scheme 1).



4	Y-Z	X	Ar	R	Yield[a]/%
a		O	4-$NO_2C_6H_4$	Cy	91
b		O	C_6H_5	Cy	89
c		O	4-BrC_6H_4	*t*-Bu	90
d		O	C_6H_5	*t*-Bu	88
e		O	4-BrC_6H_4	Cy	89
f		O	4-$NO_2C_6H_4$	*t*-Bu	92
g		C	4-ClC_6H_4	Cy	90
h		C	4-BrC_6H_4	*t*-Bu	89
i		C	4-ClC_6H_4	*t*-Bu	91

[a]Isolated yields.

Scheme 1 Three-component reaction between 4-hydroxycoumarin or 5,5-dimethyl-1,3-cyclohexandione, arylglyoxals and isocyanides.

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The structures of compounds **4a-i** were deduced from their elemental analyses and their IR, ^{1}H NMR, ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at the appropriate *m/z* values. The ^{1}H NMR spectrum of **4a** consisted of multiplet signals for the cyclohexyl ring (δ = 1.25–2.18 ppm) and a multiplet for N–CH of cyclohexyl ring (δ = 3.98 ppm). Aromatic protons resonated at δ = 7.26–8.29 ppm and a fairly broad doublet (δ = 8.89 ppm, $^3J_{HH}$ = 8.2 Hz) was observed for the NH proton. The presence of an amine proton is confirmed by exchange with D_2O indicating an exchangeable proton. The ^{1}H-decoupled ^{13}C NMR spectrum of **4a** showed 20 distinct resonances, partial assignment of these resonances is given in the Experimental section. The IR spectrum of compound **4a** exhibited an absorption band at 3245 cm^{-1} for NH group and strong broad absorptions about 1739 and 1644 cm^{-1} for carbonyl groups.

A reasonable mechanism for the formation of compounds **4** is presented in Scheme 2. The first step may involve adduct formation by Knoevenagel condensation of 4-hydroxycoumarin or 5,5-dimethyl-1,3-cyclohexandione with arylglyoxal to give the intermediate **5**. The next step of this mechanism could involve the [4 + 1] cycloaddition reaction of the electron-deficient heterodiene moiety of adduct **5** with the isocyanide to afford an iminolactone intermediate **6** which then undergoes a [1, 3]-H shift to yield the furocoumarin or benzofuran as the end product.

In summary, we report a simple and efficient one-pot synthesis of 2-alkylamino-3-(aryl)-furo[3,2-*c*]chromen-4-one or 3-(aryl)-2-alkylamino-6,6-dimethyl-6,7-dihydro-5*H*-benzofuran-4-one derivatives by three-component reaction between 4-hydroxycoumarin or 5,5-dimethyl-1,3-cyclohexandione, arylglyoxals, and alkyl isocyanides. The advantage of this method is that the reaction is carried out under neutral conditions and simply available starting materials are used without any purification or modification.

Experimental

Melting points were determined with an electrothermal 9100 apparatus. Elemental analyses were performed at analytical laboratory of Islamic Azad University, Yazd branch using a Costech ECS 4010 CHNS-O analyser. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionisation potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker DRX-300 Avance spectrometer at solution in $CDCl_3$ using TMS as internal standard. The chemicals used in this work purchased from Fluka (Buchs, Switzerland) were used without further purification.

General procedure

A solution of 4-hydroxycoumarin or 5,5-dimethyl-1,3-cyclohexandione (1 mmol), arylglyoxal (1 mmol) and alkyl isocyanide (1 mmol) in acetonitrile (10 mL) was refluxed for 5 h. The solvent was removed under reduced pressure, and the residue was separated by column chromatography (silica gel, hexane–*EtOA*c, 5 : 1) to afford the pure title compounds.

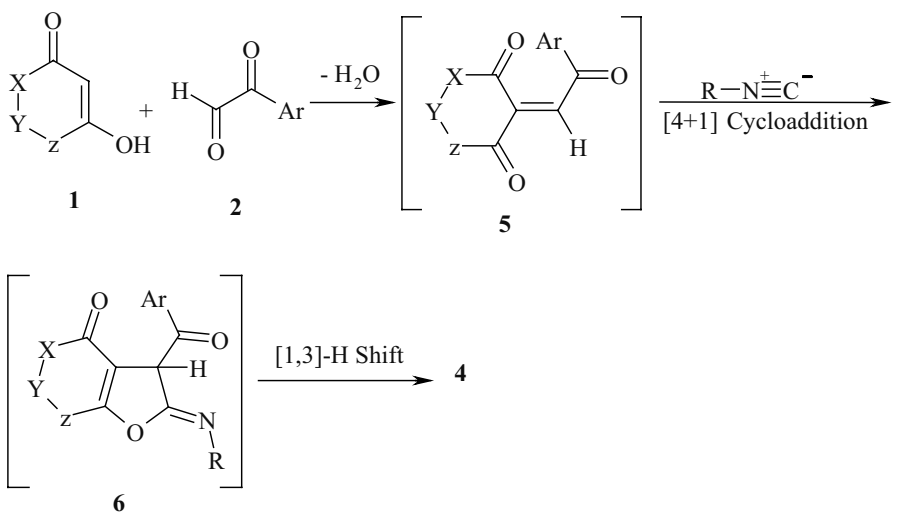
2-Cyclohexylamino-3-(4-nitro-benzoyl)-furo[3,2-c]chromen-4-one **(4a)**: Yellow crystals, (0.39 g, 91%). M.p. 208–210 °C. IR (KBr) (ν_{max}, cm^{-1}): 3245 (N–H), 1739, 1644 (C=O). MS (*m/z*,%): 432 (M$^+$, 10). Anal. Calcd for $C_{24}H_{20}N_2O_6$ (432) C, 66.66; H, 4.66; N, 6.48. Found: C, 66.54; H, 4.62; N, 6.37%. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.25–2.18 (10 H, m, 5 CH_2), 3.98 (1 H, m, N–CH), 7.26–8.29 (8 H, m, arom), 8.89 (1 H, d, $^3J_{HH}$ = 8.2 Hz, NH···O=C), ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 23.32, 24.13 and 32.12 (5 CH_2), 50.99 (N–CH), 92.48, 107.01, 110.60, 115.83, 119.14, 121.83, 123.57, 128.06, 129.85, 145.10, 147.92, 148.63, 150.76 and 155.13 (arom. and 2 C=C), 163.92, 186.11(C=O) ppm.

3-Benzoyl-2-cyclohexylamino-furo[3,2-c]chromen-4-one **(4b)**: Yellow crystals, (0.34 g, 89%). M.p. 165–167 °C. IR (KBr) (ν_{max}, cm^{-1}): 3270 (N–H), 1676, 1604 (C=O). MS (*m/z*,%): 387 (M$^+$, 5). Anal. Calcd for $C_{24}H_{21}NO_4$ (387) C, 74.40; H, 5.46; N, 3.62. Found: C, 74.32; H, 5.40; N, 3.51%. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.25–2.16 (10 H, m, 5 CH_2), 3.93 (1 H, m, N–CH), 7.25–7.80 (9 H, m, arom), 8.71 (1 H, d, $^3J_{HH}$ = 8.2 Hz, NH···O=C), ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 24.45, 25.32 and 33.30 (5 CH_2), 51.86 (N-CH), 93.42, 108.91, 111.92, 116.80, 120.03, 124.36, 127.62, 128.56, 129.63, 131.36, 140.58, 149.13, 151.79 and 156.11 (arom. and 2 C=C), 164.74, 189.62 (C=O) ppm.

3-(4-Bromo-benzoyl)-2-tert-butylamino-furo[3,2-c]chromen-4-one **(4c)**: Red crystals, (0.39 g, 90%). M.p. 145–146 °C. IR (KBr) (ν_{max}, cm^{-1}): 3420 (N–H), 1742, 1640 (C=O). MS (*m/z*,%): 439 (M$^+$, 11). Anal. Calcd for $C_{22}H_{18}BrNO_4$ (439) C, 60.01; H, 4.12; N, 3.18. Found: C, 60.22; H, 4.11; N, 3.12%. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.61 (9 H, s, CMe_3), 7.33–7.78 (8 H, m, arom), 9.03 (1 H, br, NH···O=C), ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 30.22 (C*Me*$_3$), 53.87 (*C*Me$_3$), 93.92, 108.91, 111.86, 116.91, 124.51, 125.92, 129.92, 130.13, 130.85, 132.55, 139.26, 149.68, 151.76 and 156.31 (arom. and 2 C=C), 165.12, 188.32 (C=O) ppm.

3-Benzoyl-2-tert-butylamino-furo[3,2-c]chromen-4-one **(4d)**: Yellow oil, (0.31 g, 88%). IR (KBr) (ν_{max}, cm^{-1}): 3315 (N–H), 1688, 1618 (C=O). MS (*m/z*,%): 361 (M$^+$, 6). Anal. Calcd for $C_{22}H_{19}NO_4$ (361) C, 73.12; H, 5.30; N, 3.88. Found: C, 73.08; H, 5.36; N, 3.82%. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.62 (9 H, s, CMe_3), 7.26–7.66 (9 H, m, arom), 9.06 (1 H, br, NH···O=C), ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 29.83 (C*Me*$_3$), 53.76 (*C*Me$_3$), 94.83, 111.92, 116.83, 119.92, 124.45, 127.64, 128.43, 128.82, 129.66, 133.46, 135.20, 140.42, 149.86, 151.72 and 156.11 (arom. and 2 C=C), 165.08, 189.86 (C=O) ppm.

3-(4-Bromo-benzoyl)-2-cyclohexylamino-furo[3,2-c]chromen-4-one **(4e)**: Yellow crystals, (0.41 g, 89%). M.p. 120–122 °C. IR (KBr) (ν_{max}, cm^{-1}): 3485 (N–H), 1739, 1642 (C=O). MS (*m/z*,%): 465 (M$^+$, 9). Anal. Calcd for $C_{24}H_{20}BrNO_4$ (465) C, 61.81; H, 4.32; N, 3.00. Found: C, 61.78; H, 4.35; N, 3.09%.^{1}H NMR (300.1 MHz, $CDCl_3$):



Scheme 2 Suggested mechanism for formation of compounds **4a–i.**

δ = 1.26–2.17 (10 H, m, 5 CH_2), 3.95 (1 H, m, N–CH), 7.26–7.80 (8 H, m, arom), 8.73 (1 H, d, $^3J_{HH}$ = 8.2 Hz, NH···O=C), ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 24.68, 25.24 and 33.21 (5 CH_2), 51.86 (N–CH), 93.11, 108.54, 111.74, 116.70, 120.06, 124.42, 125.85, 129.71, 130.12, 130.70, 139.21, 149.22, 151.67 and 156.12 (arom. and 2 C=C), 164.85, 188.16(C=O) ppm.

2-t-Butylamino-3-(4-nitro-benzoyl)-furo[3,2-c]chromen-4-one **(4f)**: Yellow crystals, (0.37 g, 92%). M.p. 150–151 °C. IR (KBr) (ν_{max}, cm^{-1}): 3325 (N–H), 1680, 1623 (C=O). MS (*m/z*,%): 406 (M^+, 6). Anal. Calcd for $C_{22}H_{18}N_2O_6$ (406) C, 65.02; H, 4.46; N, 6.89. Found: C, 65.11; H, 4.39; N, 6.85%. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.64 (9 H, s, CMe_3), 7.26–8.37 (9 H, m, arom), 9.19 (1 H, br, NH···O=C), ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 30.34 (*C*Me_3), 54.14 (*C*Me_3), 94.11, 111.76, 117.05, 120.08, 123.03, 124.62, 128.82, 129.06, 130.22, 138.93, 146.28, 149.06, 150.07 and 151.83 (arom. and 2 C=C), 165.32, 187.33 (C=O) ppm.

3-(4-Chloro-benzoyl)-2-cyclohexylamino-6,6-dimethyl-6,7-dihydro-5H-benzofuran-4-one **(4g)**: Yellow crystals, (0.35 g, 90%). M.p. 92–93 °C. IR (KBr) (ν_{max}, cm^{-1}): 3275 (N–H), 1724, 1678 (C=O). MS (*m/z*,%): 399 (M^+, 6). Anal. Calcd for $C_{23}H_{26}ClNO_3$ (399) C, 69.08; H, 6.55; N, 3.50. Found: C, 69.26; H, 6.49; N, 3.52%. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.13 (6 H, s, 2CH_3), 1.20–2.17 (10 H, m, 5 CH_2), 2.25 (2H, s, CH_2), 2.70 (2H, s, CH_2), 3.72 (1 H, m, N–CH), 7.27–7.47 (4 H, m, arom), 8.46 (1 H, d, $^3J_{HH}$ = 8.2 Hz, NH···O=C) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 23.44, 24.27 and 32.34 (5 CH_2), 27.41 (2CH_3), 34.05, 37.01(2CH_2), 50.39 (*C* $(CH_3)_2$), 51.67 (N-CH), 91.91, 116.94, 126.54, 128.66, 135.42, 138.71, 156.82 and 163.32 (arom. and 2 C=C), 186.95, 190.72 (C=O) ppm.

3-(4-Bromo-benzoyl)-2-tert-butylamino-6,6-dimethyl-6,7-dihydro-5H-benzofuran-4-one **(4h)**: Yellow crystals, (0.37 g, 89%). M.p. 96–98 °C IR (KBr) (ν_{max}, cm^{-1}): 3315 (N–H), 1680, 1637 (C=O). MS (*m/z*,%): 417 (M^+, 6). Anal. Calcd for $C_{21}H_{24}BrNO_3$ (417) C, 60.29; H, 5.78; N, 3.35. Found: C, 60.41; H, 5.61; N, 3.33%. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.14 (6 H, s, 2CH_3), 1.48 (9 H, s, CMe_3), 2.30 (2H, s, CH_2), 2.73 (2H, s, CH_2), 7.26–7.49 (4 H, m, arom), 8.80 (1 H, br, NH···O=C), ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 27.44 (2CH_3), 28.76 (*C*Me_3), 34.05, 36.04 (2CH_2), 51.67 (*C*$(CH_3)_2$), 51.99 (*C*Me_3), 92.73, 116.53, 124.45, 128.74, 129.52, 139.1, 156.94, and 163.65 (arom. and 2 C=C), 187.12, 190.75 (C=O) ppm.

2-t-Butylamino-3-(4-chloro-benzoyl)-6,6-dimethyl-6,7-dihydro-5H-benzofuran-4-one **(4i)**: Yellow crystals, (0.33 g, 91%). M.p. 101–102 °C. IR (KBr) (ν_{max}, cm^{-1}): 3345 (N–H), 1680, 1633 (C=O). MS (*m/z*,%): 373 (M^+, 6). Anal. Calcd for $C_{21}H_{24}ClNO_3$ (373) C, 67.46; H, 6.47; N, 3.75. Found: C, 67.42; H, 6.31; N, 3.71%. ^{1}H NMR (300.1 MHz, $CDCl_3$) δ = 1.14 (6 H, s, 2CH_3), 1.49 (9 H, s, CMe_3), 2.31 (2H, s, CH_2), 2.73 (2H, s, CH_2), 7.27–7.47 (4 H, m, arom), 8.79 (1 H, br, NH···O=C), ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 27.36 (2CH_3), 28.77 (*C*Me_3), 34.06, 36.07 (2CH_2), 51.70 (*C*$(CH_3)_2$), 51.98 (*C*Me_3), 92.75, 116.55, 126.65, 128.52, 135.42, 138.72, 156.92 and 163.63 (arom. and 2 C=C), 187.07, 190.62 (C=O) ppm.

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