SHORT PAPER

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Microwave-assisted rapid synthesis of furan annulated heterocycles†

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The one-pot three-component condensation reactions of 4-hydroxycoumarin or 4-hydroxy-6-methylpyrone **1**, *p*-substituted benzaldehydes **2** and alkyl or aryl isocyanides **3** to afford furan annulated heterocycles, in high yields after 3 minutes under microwave irradiation, are reported.

Keywords: furan, furocoumarin, isocyanide, three-component

Furocoumarins are an important class of heterocyclic compounds possessing anticoagulant, insecticide, anthelminthic, hypnotic, antifungal, and HIV protease inhibition activity.[1-3] Although there are several methods available for the synthesis of furocoumarins[4-8] and furopyranones,[9] their application has been limited by difficulties in controlling the regiochemistry of the linear and angular adduct.[4,5] Hence multi-step reactions,[6,7] involving long reaction times at high temperature[6-8] and by-products formation[9] have been used.

Very recently, Nair have reported a one-pot synthesis of furocoumarins and furopyranones.[8] However the reaction times up to 12–24 h were required under refluxing conditions in benzene which is a very toxic solvent.

In continuation of our interest on microwave-assisted organic transformation[10-12] and chemistry of isocyanides leading to the furan derivatives synthesis,[13-15] herein we describe an efficient and high yielding protocol for the preparation of furocoumarin and furopyranone derivatives.

The one-pot three component condensation reactions of 4-hydroxycoumarin or 4-hydroxy-6-methylpyrone **1**, *p*-substituted benzaldehydes **2** and alkyl or aryl isocyanides **3** proceeded spontaneously in DMF under microwave irradiation and were complete within 3 min. The ^{1}H and ^{13}C NMR spectra of the crude products clearly indicated the formation furocoumarins and furopyrons **4**. Any product other than **4** could not be detected by NMR spectroscopy. The structure of the new compounds **4a–i** was deduced from their elemental analyses and their IR, ^{1}H NMR and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks or M+1 peaks at the appropriate *m/z* values.

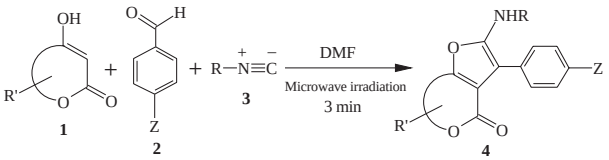
In summary, the microwave-assisted irradiation method for the synthesis of furocoumarins and furopyranones at 3 min, makes this reaction an interesting and efficient protocol alternative to reported approach at 12–24 h under refluxing conditions in toxic benzene.

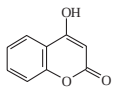
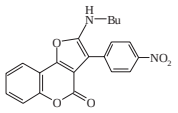
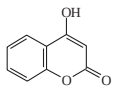
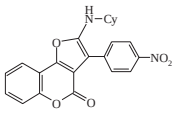
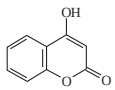
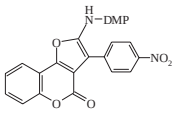
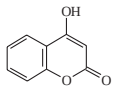
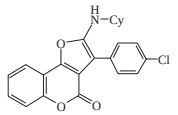
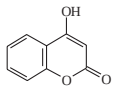
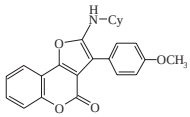
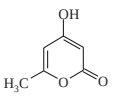
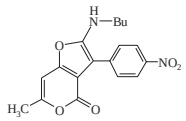
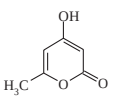
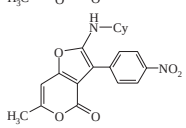
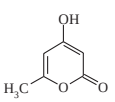
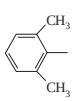
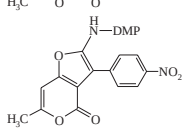
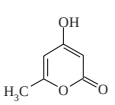
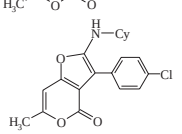
Experimental

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Elemental analyses were performed using a Heraeus CHN–O–Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER DRX-500 AVANCE spectrometer at 500.13 and 125.77 MHz, respectively. NMR spectra were obtained on solutions in $CDCl_3$ using TMS as internal standard. The isocyanides used in this work were purchased from Fluka (Buchs, Switzerland) chemical company.

Typical procedure for the preparation of 2-(tert-butylamino)-3-(4-nitrophenyl)-4H-furo[3,2c]chromen-4-one (4a): To a mixture of 4-hydroxycoumarin (0.162 g, 1 mmol) and 4-nitrobenzaldehyde (0.151 g, 1 mmol) in DMF (1 ml) was added *tert*-butyl isocyanide (0.084 g, 1 mmol) via a syringe. The mixture was then irradiated at medium high power for 3 min in a domestic microwave oven. After cooling to room

Table 1



4	Coumarin or Pyrone	Z	R	Product	Yield /%
a		NO_2			84
b		NO_2			94
c		NO_2			92
d		Cl			85
e		OCH_3			90
f		NO_2			81
g		NO_2			88
h		NO_2			91
i		Cl			79

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

temperature, the solvent was removed under vacuum and the residue was treated with diethyl ether to afford a red powder which was recrystallised from CH_2Cl_2:n-hexane (1:3) to give a crystalline solid. The resulting red crystals were filtered and washed with *n*-hexane (3×10 ml) to yield **4a** as red crystals (0.318 g, 84 %). M.p. 166–168 °C. IR (KBr) (ν_{max}/cm^{-1}): 3295 (N–H), 1730 (C=O), 1509 and 1332 (NO_2). ^{1}H NMR ($CDCl_3$, Me_4Si): δ_H 1.44 (9 H, s, $C(CH_3)_3$), 4.41 (1 H, br s, NH), 7.34 and 7.80 (4 H, m, C_6H_4), 7.70 and 8.27 (4 H, 2 d, $^3J_{HH}$=8.7 Hz, $C_6H_4NO_2$). ^{13}C NMR ($CDCl_3$, Me_4Si): δ_C 30.41 (CMe_3), 54.39 (CMe_3), 99.46, 109.67, 112.42, 117.09, 119.81, 123.91, 124.53, 129.62, 130.48, 138.10, 146.08, 151.33, 151.66 and 155.59 (arom. and 2 C=C), 157.72 (C=O). MS (*m/z*, %) 378 (M^+, 20), 323 (100), 305 (12), 276 (78), 121 (98), 83 (11), 55 (65). Anal. Calcd. for $C_{21}H_{18}N_2O_5$ (378.41): C, 66.65; H, 4.79; N, 7.40%. Found: C, 66.71; H, 4.85; N, 7.31%.

2-(Cyclohexylamino)-3-(4-nitrophenyl)-4H-furo[3,2c]chromen-4-one (4b): Red crystals, (0.381 g, 94 %). M.p. 169–171 °C. IR (KBr) ($\nu_{max,}$ cm^{-1}): 3320 (N–H), 1724 (C=O), 1513 and 1337 (NO_2). ^{1}H NMR ($CDCl_3$, Me_4Si): δ_H 1.32–2.11 (10 H, m, 5 CH_2), 3.67 (1 H, m, N–CH), 4.62 (1 H, d, $^3J_{HH}$= 6.9 Hz, NH), 7.26–7.78 (4 H, m, C_6H_4), 7.69 and 8.22 (4 H, 2 d, $^3J_{HH}$=8.7 Hz, $C_6H_4NO_2$). ^{13}C NMR ($CDCl_3$, Me_4Si): δ_C 24.85, 25.43 and 34.04 (5 CH_2), 53.45 (N-CH), 94.55, 110.28, 112.40, 116.94, 116.94, 119.62, 123.86, 124.46, 129.23, 138.32, 145.59, 150.31, 151.35 and 155.69 (arom. and 2 C=C), 157.79 (C=O). MS (*m/z*, %) 404 (M^+, 100), 322 (52), 305 (12), 275 (10), 121 (10), 83 (13), 55 (75). Anal. Calcd. for $C_{23}H_{20}N_2O_5$ (404.45): C, 68.30; H, 4.98; N, 6.93%. Found: C, 68.19; H, 5.05; N, 7.03%.

2-(2,6-dimethylphenylamino)-3-(4-nitrophenyl)-4H-furo[3,2c]chromen-4-one (4c): Red crystals, (0.393 g, 92 %). M.p. 207–209 °C. IR (KBr) ($\nu_{max,}$ cm^{-1}): 3320 (N–H), 1729 (C=O), 1502 and 1333 (NO_2). ^{1}H NMR ($CDCl_3$, Me_4Si): δ_H 2.23 (6 H, s, $C_6H_3Me_2$), 6.09 (1 H, br s, NH), 7.04–8.16 (11 H, m, arom.). ^{13}C NMR ($CDCl_3$, Me_4Si): δ_C 18.49 ($C_6H_3Me_2$), 99.69, 112.23, 117.04, 119.96, 123.34, 124.48, 126.45, 127.58, 128.89, 129.63, 129.72, 130.48, 133.51, 135.16, 137.06, 150.99, 151.69 and 152.55 (arom. and 2 C=C), 157.64 (C=O). MS (*m/z*, %) 426 (M^+, 10), 322 (5), 249 (18), 121 (30), 83 (12), 55 (25). Anal. Calcd. for $C_{25}H_{18}N_2O_5$ (426.46): C, 70.41; H, 4.25; N, 6.57%. Found: C, 70.47; H, 4.18; N, 6.66%.

2-(cyclohexylamino)-3-(4-chlorophenyl)-4H-furo[3,2c]chromen-4-one **(4d):** Yellow crystals, (0.335 g, 85 %). M.p. 96–98 °C. IR (KBr) ($\nu_{max,}$ cm^{-1}): 3330 (N–H), 1705 (C=O), 1593 (C=C). ^{1}H NMR ($CDCl_3$, Me_4Si): δ_H 0.88–2.06 (10 H, m, 5 CH_2), 3.57 (1 H, m, N–CH), 4.21 (1 H, d, $^3J_{HH}$= 7.1 Hz, NH), 7.25–7.78 (8 H, m, arom.). ^{13}C NMR ($CDCl_3$, Me_4Si): δ_C 24.86, 25.50 and 34.12 (5 CH_2), 53.64 (N-CH), 96.38, 110.72, 112.47, 116.94, 119.53, 124.26, 128.79, 128.82, 129.20, 130.47, 132.54, 149.96, 151.34 and 154.86 (arom. and 2 C=C), 157.96 (C=O). MS (*m/z*, %) 393 (M^+, 43), 311 (100), 275 (12), 163 (22), 121 (27), 83 (10), 55 (75). Anal. Calcd. For $C_{23}H_{20}ClNO_3$ (393.86): C, 70.14; H, 5.12; N, 3.56%. Found: C, 70.20; H, 5.05; N, 3.51%.

2-(cyclohexylamino)-3-(4-methoxyphenyl)-4H-furo[3,2c]chromen-4-one **(4e):** Yellow crystals, (0.351 g, 90 %). M.p. 133–135 °C. IR (KBr) ($\nu_{max,}$ cm^{-1}): 3340 (N–H), 1714 (C=O), 1599 (C=C). ^{1}H NMR ($CDCl_3$, Me_4Si): δ_H 1.19–2.06 (10 H, m, 5 CH_2), 3.53 (1 H, m, N–CH), 3.83 (3 H, s, OCH_3), 4.15 (1 H, d, $^3J_{HH}$= 8.2 Hz, NH), 6.97–7.77 (8 H, m, arom.). ^{13}C NMR ($CDCl_3$, Me_4Si): δ_C 24.90, 25.56 and 34.15 (5 CH_2), 53.82 (N-CH), 55.29 (OCH_3), 97.78, 111.04, 112.93, 114.17, 116.89, 119.48, 122.80, 124.13, 128.50, 130.46, 149.73, 151.32, 154.62 and 158.04 (arom. and 2 C=C), 158.53 (C=O). MS (*m/z*, %) 389 (M^+, 65), 307 (100), 278 (25), 159 (41), 121 (24), 83 (5), 55 (50). Anal. Calcd. for $C_{24}H_{23}NO_4$ (389.44): C, 74.02; H, 5.95; N, 3.60%. Found: C, 73.88; H, 6.03; N, 3.66%.

2-(tert-butylamino)-6-methyl-3-(4-nitrophenyl)-4H-furo[3,2c]pyran-4-one (4f): Red crystals, (0.278 g, 81 %). M.p. 162–164 °C. IR (KBr) ($\nu_{max,}$ cm^{-1}): 3280 (N–H), 1716 (C=O), 1506 and 1334 (NO_2). ^{1}H NMR ($CDCl_3$, Me_4Si): δ_H 1.33 (9 H, s, $C(CH_3)_3$), 2.34 (3 H, s, CH_3), 4.12 (1 H, br s, NH), 6.39 (1 H, s, C=CH), 7.70 and 8.24 (4 H, 2 d, $^3J_{HH}$=8.6 Hz, $C_6H_4NO_2$). ^{13}C NMR ($CDCl_3$, Me_4Si): δ_C 20.11 (CH_3), 30.37 (CMe_3), 54.30 (CMe_3), 95.30, 99.64, 107.27, 123.81, 129.44, 138.35, 145.92, 154.24, 156.50 and 158.32 (arom. and 3 C=C), 159.37 (C=O). MS (*m/z*, %) 343 (MH^+, 20), 288 (35), 305 (5), 57 (100). Anal. Calcd. for $C_{18}H_{18}N_2O_5$ (342.38): C, 63.14; H, 5.30; N, 8.18%. Found: C, 63.21; H, 5.21; N, 8.26%.

2-(cyclohexylamino)-6-methyl-3-(4-nitrophenyl)-4H-furo[3,2c]pyran-4-one (4g): Red crystals, (0.325 g, 88 %). M.p. 165–167 °C. IR (KBr) ($\nu_{max,}$ cm^{-1}): 3275 (N–H), 1704 (C=O), 1578 and 1322 (NO_2). ^{1}H NMR ($CDCl_3$, Me_4Si): δ_H 1.18–2.02 (10 H, m, 5 CH_2), 2.32 (3 H, s, CH_3), 3.51 (1 H, m, N–CH), 4.43 (1 H, br s, NH), 6.34 (1 H, s, C=CH), 7.65 and 8.19 (4 H, 2 d, $^3J_{HH}$=8.5 Hz, $C_6H_4NO_2$). ^{13}C NMR ($CDCl_3$, Me_4Si): δ_C 20.06 (CH_3), 24.83, 25.42 and 34.10 (5 CH_2), 53.33 (N-CH), 93.53, 95.18, 107.92, 123.85, 128.87, 138.64, 145.32, 154.53, 155.51 and 157.56 (3 C=C and $C_6H_4NO_2$), 159.49 (C=O). MS (*m/z*, %) 369 (MH^+, 60), 287 (100), 270 (95), 240 (65), 83 (97), 55 (60). Anal. Calcd. for $C_{20}H_{20}N_2O_5$ (368.42): C, 65.20; H, 5.47; N, 7.60%. Found: C, 65.08; H, 5.53; N, 7.67%.

2-(2,6-dimethylphenylamino)-6-methyl-3-(4-nitrophenyl)-4H-furo[3,2c]pyran-4-one (4h): Red crystals, (0.305 g, 91 %). M.p. 163–165 °C. IR (KBr) ($\nu_{max,}$ cm^{-1}): 3270 (N–H), 1715 (C=O), 1502 and 1335 (NO_2). ^{1}H NMR ($CDCl_3$, Me_4Si): δ_H 2.19 (6 H, s, $C_6H_3Me_2$), 2.30 (3 H, s, CH_3), 6.15 (1 H, br s, NH), 6.28 (1 H, s, C=CH), 7.04–8.09 (7 H, m, arom.). ^{13}C NMR ($CDCl_3$, Me_4Si): δ_C 18.42 ($C_6H_3Me_2$), 20.07 (CH_3), 95.30, 96.23, 107.83, 123.34, 126.18, 128.84, 129.34, 133.44, 135.64, 137.64, 145.57, 151.66, 156.14 and 158.40 (3 C=C and arom.), 159.46 (C=O). MS (*m/z*, %) 391 (MH^+, 90), 361 (5), 105 (40), 77 (56). Anal. Calcd. for $C_{22}H_{18}N_2O_5$ (390.42): C, 67.68; H, 6.63; N, 7.17%. Found: C, 67.74; H, 6.71; N, 7.11%.

2-(cyclohexylamino)-6-methyl-3-(4-chlorophenyl)-4H-furo[3,2c]pyran-4-one (4i): Brown crystals, (0.315 g, 88 %). M.p. 118–120 °C. IR (KBr) ($\nu_{max,}$ cm^{-1}): 3265 (N–H), 1715 (C=O), 1598 (C=C). ^{1}H NMR ($CDCl_3$, Me_4Si): δ_H 1.16–2.31 (10 H, m, 5 CH_2), 2.31 (3 H, s, CH_3), 3.42 (1 H, m, N–CH), 4.05 (1 H, br s, NH), 6.33 (1 H, s, C=CH), 7.36 and 7.44 (4 H, 2 d, $^3J_{HH}$=8.5 Hz, C_6H_4Cl). ^{13}C NMR ($CDCl_3$, Me_4Si): δ_C 20.05 (CH_3), 24.85, 25.50 and 34.15 (5 CH_2), 53.63 (N-CH), 95.26, 95.53, 108.30, 128.74, 129.53, 130.22, 132.18, 153.45, 155.21 and 156.98 (3 C=C and C_6H_4Cl), 159.64 (C=O). MS (*m/z*, %) 357 (M^+, 48), 275 (100), 204 (10), 83 (10), 55 (75). Anal. Calcd. for $C_{20}H_{20}ClNO_3$ (357.83): C, 67.13; H, 5.63; N, 3.91%. Found: C, 67.08; H, 5.76; N, 4.03%.

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References

1 G. Feuer, *Progress in Medicinal Chemistry*, G.P. Ellis and G.B. West, Eds.; North-Holland: New York, 1974.
2 A.A. Deana, *J. Med. Chem.*, 1983, **26**, 580.
3 E. Wenkert and B.L. Buckwalter, *J. Am. Chem. Soc.*, 1972, **94**, 4367.
4 S. Tollari, G. Palmisano, S. Cenini, G. Cravotto, G.B. Giovenzana and A. Penoni, *Synthesis*, 2001, 735.
5 G. Appendino, G. Cravotto, G. Palmisano and R. Annunziata, *Tetrahedron*,1998, **54**, 10819.
6 Y.R. Lee, B.S. Kim and H.C. Wang, *Tetrahedron*, 1998, **54**, 12215.
7 Y.R. Lee and J.Y. Suk, *Tetrahedron*, 2002, **58**, 2359.
8 V. Nair, R.S. Menon, A.U. Vinod and S. Viji, *Tetrahedron Lett.*, 2002, **43**, 2293.
9 K. Kobayashi, K. Sakashita, H. Akamatsu, K. Tanaka, T. Uneda, T. Kitamura, O. Morikawa and H. Konishi, *Heterocycles*, 1999, **51**, 2881.
10 A. Shaabani, *J. Chem. Res.(S)*, 1998, 672.
11 A. Shaabani, A. Bazgir, F. Teimouri and D.G. Lee, *Tetrahedron Lett.*, 2002, **43**, 5165.
12 A. Shaabani, N. Safari, A. Bazgir, F. Bahadoran and P. Rajabali Jamaat, *Synth. Commun.*, 2003, **33**, 1717.
13 I. Yavari, A. Shaabani and M.T. Maghsoodlou, *Monatsh. Chem.*, 1997, **128**, 697.
14 A. Shaabani, S. Ajabi, F. Farrokhzad and H.R. Bijanzadeh, *J. Chem. Res.(S)*, 1999, 582.
15 A. Shaabani, M.B. Teimouri and H.R. Bijanzadeh, *Tetrahedron Lett.*, 2002, **43**, 9151.