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One-pot Three-component Condensation Reactions in Water. An Efficient and Improved Procedure for the Synthesis of Furan Annulated Heterocycles

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Summary. The environment-friendly one-pot three-component condensation reactions of 4-hydroxycoumarin or 4-hydroxy-6-methylpyrone, *p*-substituted benzaldehyde, and alkyl or aryl isocyanides to afford furocoumarines or furopyranones in water in good yields after about one hour at 75°C are reported.

Keywords. Furocoumarine; Furopyranone; Isocyanide; *p*-Substituted benzaldehyde; Three-component.

Introduction

For the synthetic chemist, water often appears as a natural enemy to be kept away from the reaction mixture until workup. Nevertheless, in recent years reports have appeared in increasing number describing the deliberate use of water as a solvent for various organic reactions [1]. In 1980, *Rideout* and *Breslow* [2] rediscovered a rate increase by a factor of more than 700 when the *Diels-Alder* reaction is performed in water instead of hydrocarbons. *Breslow* explained his results on the basis of hydrophobic interactions that induce a favorable aggregation of the apolar components in the polar water [3]. Further reasons that make water unique compared to other organic solvents are that it is cheap, not inflammable, and more important, it is not toxic. Choice of solvents is one of the problems to face in order to perform eco-efficient processes.

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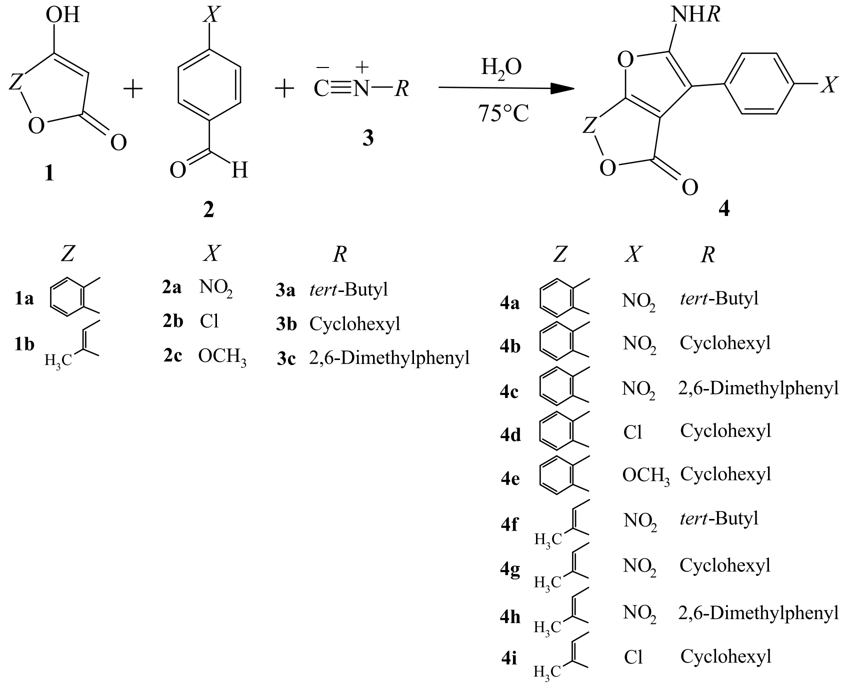
Recently, *Nair* [4] reported the synthesis of furocoumarins from 4-hydroxycoumarin and 4-hydroxy-6-methylpyrone, aldehydes, and cyclohexyl isocyanide in benzene under reflux conditions. Product yields were relatively good, but reaction time necessary to obtain these yields was very long, for example 12–24 h under reflux conditions in a toxic solvent such as benzene.

As a part of our program towards green synthesis [5–10], we wish to report the three-component condensation reactions of 4-hydroxycoumarin or 4-hydroxy-6-methylpyrone, *p*-substituted benzaldehyde, and alkyl or aryl isocyanides in water at 75°C.

Results and Discussion

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 at 75°C in water and were completed within about one hour (Scheme 1). Spectra, ^{1}H and ^{13}C NMR, of the crude products clearly indicated the formation of furocoumarins or furopyranones **4**. The structure of the novel compounds **4a**–**4i** 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.

The ^{1}H NMR spectrum of **4a** exhibited one single sharp line readily recognized as arising from *tert*-butyl ($\delta = 1.45$ ppm). A fairly broad singlet ($\delta = 4.43$ ppm) is observed for the NH group. The aromatic hydrogens give rise to characteristic signals in the aromatic region of the spectrum ($\delta = 7.33$–8.27 ppm). The ^{1}H decoupled ^{13}C NMR spectrum of **4a** showed 17 distinct resonances in agreement



Scheme 1

with the suggested structure. Partial assignment of these resonances is given in the Experimental.

In summary, using water as an eco-compatible reaction solvent replacing toxic benzene and decreasing reaction times from 12–24 h to about 1 h makes it an interesting and efficient alternative to the reported procedure [4].

Experimental

Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses were performed using a Heraeus CHN–O-Rapid analyzer. These results were in full agreement with the calculated values. 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).

Typical Procedure for the Preparation of ***4a***

To a magnetically stirred mixture of 0.162 g of 4-hydroxycoumarin (1 mmol) and 0.151 g of 4-nitrobenzaldehyde (1 mmol) in 20 cm^3 of H_2O 0.084 g of *tert*-butyl isocyanide (1 mmol) was added *via* a syringe and heated for 75 min at 75°C. After cooling to room temperature, the resulting red precipitate was filtered and washed with 50 cm^3 of H_2O. The solid residue was dried and crystallized from CH_2Cl_2:*n*-hexane = 1:3 to yield 0.299 g of **4a** as red crystals (79%).

2-(tert-Butylamino)-3-(4-nitrophenyl)-4H-furo[3,2-c]chromen-4-one
(**4a**, $C_{21}H_{18}N_2O_5$)

Mp 165–167°C; IR (KBr): $\bar{\nu} = 3300$ (N–H), 1730 (C=O), 1506 and 1332 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$, *TMS*): $\delta = 1.45$ (s, $C(CH_3)_3$), 4.43 (br s, NH), 7.33 and 7.78 (m, C_6H_4), 7.71 and 8.27 (2d, $J = 8.7$ Hz, $C_6H_4NO_2$) ppm; ^{13}C NMR ($CDCl_3$, *TMS*): $\delta = 30.41$ (CMe_3), 54.40 (CMe_3), 99.46, 109.67, 112.43, 117.10, 119.82, 123.91, 124.53, 129.63, 130.48, 138.10, 146.09, 151.34, 151.66, and 155.59 (arom. C and 2C=C), 157.72 (C=O) ppm; MS: m/z (%) = 378 (M$^+$, 31), 323 (100), 305 (20), 276 (71), 249 (68), 121 (93), 92 (90), 83 (8), 55 (53).

2-(Cyclohexylamino)-3-(4-nitrophenyl)-4H-furo[3,2-c]chromen-4-one
(**4b**, $C_{23}H_{20}N_2O_5$)

Red crystals (0.344 g, 85%); mp 170–172°C; IR (KBr): $\bar{\nu} = 3325$ (N–H), 1730 (C=O), 1511 and 1333 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$, *TMS*): $\delta = 1.26$–2.11 (m, 5CH_2), 3.67 (m, N–CH), 4.62 (d, $J = 6.8$ Hz, NH), 7.27–7.78 (m, C_6H_4), 7.69 and 8.22 (2d, $J = 8.7$ Hz, $C_6H_4NO_2$) ppm; ^{13}C NMR ($CDCl_3$, *TMS*): $\delta = 24.86$, 25.43 and 34.04 (5CH_2), 53.45 (N–CH), 94.55, 110.28, 112.40, 116.95, 117.25, 119.63, 123.87, 124.47, 129.24, 138.32, 145.59, 150.31, 151.36, and 155.70 (arom. C and 2C=C), 157.80 (C=O) ppm; MS: m/z (%) = 404 (M$^+$, 100), 322 (40), 305 (21), 275 (8), 121 (10), 83 (12), 55 (74).

2-(2,6-Dimethylphenylamino)-3-(4-nitrophenyl)-4H-furo[3,2-c]chromen-4-one
(**4c**, $C_{25}H_{18}N_2O_5$)

Red crystals (0.388 g, 91%); mp 208–210°C; IR (KBr): $\bar{\nu} = 3325$ (N–H), 1730 (C=O), 1508 and 1335 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$, *TMS*): $\delta = 2.24$ (s, $C_6H_3Me_2$), 6.10 (br s, NH), 7.05–8.17 (m, arom. H) ppm; ^{13}C NMR ($CDCl_3$, *TMS*): $\delta = 18.50$ ($C_6H_3Me_2$), 99.70, 112.24, 117.04, 119.96, 123.35, 124.49, 126.45, 127.59, 128.90, 129.64, 129.73, 130.49, 133.51, 135.16, 137.06, 150.99, 151.70, and 152.55 (arom. C and 2C=C), 157.65 (C=O) ppm; MS: m/z (%) = 426 (M^+, 18), 322 (10), 249 (22), 121 (18), 83 (17), 55 (25).

2-(Cyclohexylamino)-3-(4-chlorophenyl)-4H-furo[3,2-c]chromen-4-one
(**4d**, $C_{23}H_{20}ClNO_3$)

Yellow crystals (0.308 g, 78%); mp 95–97°C; IR (KBr): $\bar{\nu} = 3325$ (N–H), 1708 (C=O), 1590 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, *TMS*): $\delta = 0.88–2.07$ (m, $5CH_2$), 3.58 (m, N–CH), 4.22 (d, $J = 7.1$ Hz, NH), 7.26–7.78 (m, arom. H) ppm; ^{13}C NMR ($CDCl_3$, *TMS*): $\delta = 24.86$, 25.50, and 34.13 ($5CH_2$), 53.65 (N–CH), 96.39, 110.72, 112.74, 116.95, 119.53, 124.26, 128.79, 128.83, 129.21, 130.48, 132.54, 149.96, 151.34, and 154.86 (arom. C and 2C=C), 157.96 (C=O) ppm; MS: m/z (%) = 393 (M^+, 43), 311 (100), 275 (12), 248 (10), 163 (22), 121 (27), 92 (10), 83 (8), 55 (75).

2-(Cyclohexylamino)-3-(4-methoxyphenyl)-4H-furo[3,2-c]chromen-4-one
(**4e**, $C_{24}H_{23}NO_4$)

Yellow crystals (0.277 g, 71%); mp 132–134°C; IR (KBr): $\bar{\nu} = 3330$ (N–H), 1717 (C=O), 1599 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, *TMS*): $\delta = 1.19–2.06$ (m, $5CH_2$), 3.53 (m, N–CH), 3.84 (s, OCH_3), 4.15 (d, $J = 8.2$ Hz, NH), 6.98–7.77 (m, arom. H) ppm; ^{13}C NMR ($CDCl_3$, *TMS*): $\delta = 24.90$, 25.56, and 34.15 ($5CH_2$), 53.82 (N–CH), 55.29 (OCH_3), 97.79, 111.04, 112.94, 114.17, 116.89, 119.48, 122.80, 124.13, 128.51, 130.46, 149.74, 151.33, 154.62, and 158.04 (arom. C and 2C=C), 158.54 (C=O) ppm; MS: m/z (%) = 389 (M^+, 55), 307 (100), 278 (22), 159 (41), 121 (25), 92 (8), 83 (5), 55 (53).

2-(tert-Butylamino)-6-methyl-3-(4-nitrophenyl)-4H-furo[3,2-c]pyran-4-one
(**4f**, $C_{18}H_{18}N_2O_5$)

Red crystals (0.285 g, 83%); mp 160–162°C; IR (KBr): $\bar{\nu} = 3405$ (N–H), 1720 (C=O), 1510 and 1330 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$, *TMS*): $\delta = 1.34$ (s, $C(CH_3)_3$), 2.35 (s, CH_3), 4.13 (br s, NH), 6.39 (s, C=CH), 7.70 and 8.24 (2d, $J = 8.6$ Hz, $C_6H_4NO_2$) ppm; ^{13}C NMR ($CDCl_3$, *TMS*): $\delta = 20.11$ (CH_3), 30.38 ($C\mathit{Me}_3$), 54.31 ($\mathit{C}Me_3$), 95.31, 99.64, 107.28, 123.82, 129.45, 138.36, 145.92, 154.25, 156.50, and 158.32 (arom. C and 3C=C), 159.38 (C=O) ppm; MS: m/z (%) = 343 (MH^+, 15), 288 (45), 305 (17), 57 (100).

2-(Cyclohexylamino)-6-methyl-3-(4-nitrophenyl)-4H-furo[3,2-c]pyran-4-one
(**4g**, $C_{20}H_{20}N_2O_5$)

Red crystals (0.299 g, 81%); mp 166–168°C; IR (KBr): $\bar{\nu} = 3435$ (N–H), 1705 (C=O), 1508 and 1322 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$, *TMS*): $\delta = 1.19–2.02$ (m, $5CH_2$), 2.33 (s, CH_3), 3.52 (m, N–CH), 4.44 (br s, NH), 6.35 (s, C=CH), 7.65 and 8.19 (2d, $J = 8.5$ Hz, $C_6H_4NO_2$) ppm; ^{13}C NMR ($CDCl_3$, *TMS*): $\delta = 20.07$ (CH_3), 24.84, 25.43, and 34.10 ($5CH_2$), 53.33 (N–CH), 93.54, 95.19, 107.92, 123.85, 128.87, 138.64, 145.33, 154.53, 155.51, and 157.56 (3C=C and $C_6H_4NO_2$), 159.50 (C=O) ppm; MS: m/z (%) = 369 (MH^+, 18), 287 (100), 270 (90), 240 (55), 169 (48), 83 (97), 55 (60).

2-(2,6-Dimethylphenylamino)-6-methyl-3-(4-nitrophenyl)-4H-furo[3,2-c]pyran-4-one
(**4h**, $C_{22}H_{18}N_2O_5$)

Red crystals (0.305 g, 78%); mp 165–167°C; IR (KBr): $\bar{\nu} = 3280$ (N–H), 1715 (C=O), 1510 and 1338 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$, *TMS*): $\delta = 2.20$ (s, $C_6H_3\mathit{Me}_2$), 2.31 (s, CH_3), 6.16 (br s, NH), 6.28 (s, C=CH), 7.04–8.10 (m, arom. H) ppm; ^{13}C NMR ($CDCl_3$, *TMS*): $\delta = 18.43$ ($C_6H_3\mathit{Me}_2$), 20.08 (CH_3), 95.31, 96.23, 107.84, 123.35, 126.19, 128.85, 129.34, 133.45, 135.64, 137.65, 145.58, 151.66, 156.14, and 158.40 (3C=C and arom. C), 159.46 (C=O) ppm; MS: m/z (%) = 391 (MH^+, 75), 361 (5), 243 (25), 105 (40), 77 (56).

2-(Cyclohexylamino)-6-methyl-3-(4-chlorophenyl)-4H-furo[3,2-c]pyran-4-one
(**4i**, $C_{20}H_{20}ClNO_3$)

Brown crystals (0.269 g, 75%); mp 119–121°C; IR (KBr) $\bar{\nu} = 3280$ (N–H), 1720 (C=O), 1590 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, *TMS*): $\delta = 1.16$–1.99 (m, $5CH_2$), 2.31 (s, CH_3), 3.42 (m, N–CH), 4.07 (br s, NH), 6.33 (s, C=CH), 7.35 and 7.43 (2d, $J = 8.5$ Hz, C_6H_4Cl) ppm; ^{13}C NMR ($CDCl_3$, *TMS*): $\delta = 20.06$ (CH_3), 24.86, 25.51, and 34.16 ($5CH_2$), 53.63 (N–CH), 95.26, 95.53, 108.30, 128.75, 129.53, 130.23, 132.19, 153.45, 155.22, and 156.98 (3C=C and C_6H_4Cl), 159.65 (C=O) ppm; MS: m/z (%) = 357 (M^+, 45), 275 (100), 204 (10), 163 (12), 83 (10), 55 (78).

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