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ORIGINAL PAPER

An efficient four-component reaction for the synthesis of chromeno[4,3-*b*]quinolone derivatives

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Abstract Chromenoquinolines have been prepared via an efficient one-pot, multi-component reaction of 4-hydroxy coumarin, aqueous ammonia, dimedone and different aldehydes.

Keywords Chromenoquinolines · 4-Hydroxy coumarin · One pot · Multi-component reaction

Introduction

The multi-component reactions (MCRs) are of considerable interest in organic synthesis since they provide a rapid access to the important structures, resembling natural products and drugs [1–4]. The advantageous features of this strategy in the facile preparation of privileged structures involve the atom economy, convergent character, diversity-generating potential and formation of several bonds in a single step. Therefore, this strategy has been widely employed by different research groups for the one-pot construction of versatile nitrogen-containing polycyclic skeletons [5–10].

Nitrogen-containing multi-cyclic compounds are interesting scaffolds because of their potential in exhibiting a wide array of bioactivities like DNA intercalators, antiplasmodial, antineoplastic, anticancer and antibacterial [11–17]. Chromenoquinoline, an important subclass of nitrogen-containing heterocycles, has shown promising activities [18–20] like anti-inflammatory, anticancer, glucocorticoid modulators, progesterone and 5-HT receptor antagonist [21–25]. These significant bioactivities are also reflected in ongoing efforts of synthetic chemists to prepare structurally different chromenoquinolines with hopes to find new therapeutically active compounds [26–36]. In this context, developing efficient and simple pathways for the synthesis of such an important framework from commercially available starting materials is a desirable challenge. Despite the effectiveness of these methods, in most of these approaches catalytic systems or synthesized starting materials have to be employed. Thereafter, we decided to examine the new pathway toward chromenoquinolines from readily available starting materials and under catalyst-free condition. In continuation of our program to develop new and efficient methods for the synthesis of heterocyclic compounds [37–43], herein, we envisaged a simple, four-component reaction for the synthesis of 10,11-dihydro-10,10-dimethyl-7-substituted-7*H*-chromeno[4,3-*b*]quinoline-6,8(9*H*,12*H*)-diones in moderate to good yields.

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Experimental

Melting points were taken on a *Kofler* hot-stage apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectrum was recorded on *Bruker FT-500*, using TMS as an internal standard. The elemental analysis was performed with an Elementar Analysen system GmbH *VarioEL* CHNS mode. Mass spectra were determined on an Agilent Technology (HP) mass spectrometer operating at an ionization potential of 70 eV. All reagents and solvents were purchased from Aldrich and Merck and used without any purification.

General procedure for the synthesis of chromeno[4,3-*b*] quinoline 5a-j

A mixture of 4-hydroxy coumarin (1 mmol) and 28–30% ammonia solution (5 mmol) in *n*-PrOH (5 mL) was refluxed for 1 h. Then, aldehyde (1 mmol) and dimedone (1 mmol) were added, and the reaction was continued at reflux temperature for another 11 h. After this time, the reaction was cooled down to room temperature. The residue was purified by column chromatography (petroleum ether/ethyl acetate 10:1).

10,11-Dihydro-10,10-dimethyl-7-phenyl-7H-chromeno [4,3-b]quinoline-6,8(9H,12H)-dione **(5a)** Pale-yellow powder (0.28 g, 76%). Mp (°C): 290–291.[36] IR (KBr) 3213, 3072, 1704, 1630, 1599, 1471, 1360, 1194, 1145, 1023, 738, 694. ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 9.70 (s, NH), 8.30 (dd, J = 7.5, 1.0 Hz, 1H), 7.62 (dt, J = 7.5, 1.0 Hz, 1H), 7.43 (t, J = 7.5 Hz, 1H), 7.36 (d, J = 7.5 Hz, 1H), 7.25 (d, J = 7.5 Hz, 2H), 7.21 (t, J = 8.0 Hz, 2H), 7.10 (t, J = 7.0 Hz, 1H), 4.97 (s, 1H), 2.67 (s, 2H), 2.27 (d, J = 16.5 Hz, 1H), 2.10 (d, J = 16.5 Hz, 1H), 1.08 (s, 3H), 0.95 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 194.5, 160.1, 152.0, 149.5, 145.7, 142.0, 131.8, 127.6, 126.1, 123.8, 122.8, 116.8, 116.6, 112.9, 110.8, 101.8, 50.1, 34.3, 32.0, 28.9, 26.5. Anal. Calcd. for $C_{24}H_{21}NO_3$: C, 77.61; H, 5.70; N, 3.77. Found: C, 77.53; H, 5.62; N, 3.89. MS: *m/z* (%) = 371 ([M]$^+$, 20), 294 (100), 238 (11), 210 (15), 97 (12), 57 (21), 43 (19).

10,11-Dihydro-7-(3-hydroxyphenyl)-10,10-dimethyl-7H-chromeno[4,3-b]quinoline-6,8(9H,12H)-dione **(5b)** Pale-yellow powder (0.27 g, 70%). Mp (°C): 190–192. IR (KBr) 3518, 3320, 1700, 1629, 1461, 1362, 1195, 1150, 1059, 756. ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 9.65 (s, NH), 9.08 (s, OH), 8.29 (d, J = 8.0 Hz, 1H), 7.63 (t, J = 7.0 Hz, 1H), 7.43 (t, J = 8.0 Hz, 1H), 7.36 (d, J = 7.0 Hz, 1H), 6.97 (t, J = 8.0 Hz, 1H), 6.68 (d, J = 1.5 Hz, 1H), 6.65 (d, J = 8.0 Hz, 1H), 6.48 (dd, J = 7.5, 1.5 Hz, 1H), 4.90 (s, 1H), 2.64 (s, 2H), 2.26 (d, J = 16.0 Hz, 1H), 2.10 (d, J = 16.0 Hz, 1H), 1.07 (s, 3H), 0.97 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 194.5, 160.2, 156.9, 151.9, 149.4, 146.9, 142.0, 131.8, 128.7, 123.9, 122.7, 118.2, 116.7, 114.8, 113.1, 113.0, 110.8, 101.7, 50.1, 34.0, 32.1, 28.9, 26.6. Anal. Calcd. for $C_{24}H_{21}NO_4$: C, 74.40; H, 5.46; N, 3.62. Found: C, 74.29; H, 5.38; N, 3.74.

10,11-Dihydro-7-(2-methoxyphenyl)-10,10-dimethyl-7H-chromeno[4,3-b]quinoline-6,8(9H,12H)-dione **(5c)** Pale-yellow powder (0.27 g, 68%). Mp (°C): 301–303.[36] IR (KBr) 3300, 1695, 1629, 1598, 1474, 1358, 1241, 1189, 1150, 1007, 749, 637. ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 9.62 (s, NH), 8.28 (d, J = 8.0 Hz, 1H), 7.60 (t, J = 7.5 Hz, 1H), 7.43 (t, J = 8.0 Hz, 1H), 7.32 (d, J = 7.5 Hz, 1H), 7.26 (dd, J = 7.5, 1.5 Hz, 1H), 7.08 (t, J = 8.0 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 6.79 (t, J = 7.5 Hz, 1H), 5.05 (s, 1H), 3.63 (s, 3H), 2.59 (s, 2H), 2.21 (d, J = 16.0 Hz, 1H), 1.98 (d, J = 16.0 Hz, 1H), 1.05 (s, 3H), 0.90 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 194.2, 159.9, 157.9, 151.9, 149.8, 142.4, 132.4, 131.5, 127.4, 123.7, 122.6, 119.6, 119.2, 116.6, 113.0, 111.3, 109.2, 100.3, 55.2, 50.2, 32.9, 31.9, 29.2, 25.9. Anal. Calcd. for $C_{25}H_{23}NO_4$: C, 74.79; H, 5.77; N, 3.49. Found: C, 74.68; H, 5.92; N, 3.28.

10,11-Dihydro-7-(4-methoxyphenyl)-10,10-dimethyl-7H-chromeno[4,3-b]quinoline-6,8(9H,12H)-dione **(5d)** Pale-yellow powder (0.29 g, 72%). Mp (°C): 261–263.[36] IR (KBr) 3220, 1689, 1641, 1605, 1508, 1468, 1363, 1257, 1193, 1030, 842, 752. ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 9.65 (s, NH), 8.30 (d, J = 7.5 Hz, 1H), 7.62 (t, J = 8.0 Hz, 1H), 7.43 (t, J = 7.5 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.15 (d, J = 7.5 Hz, 2H), 6.77 (d, J = 7.5 Hz, 2H), 4.90 (s, 1H), 3.66 (s, 3H), 2.66 (s, 2H), 2.26 (d, J = 16.0 Hz, 1H), 2.09 (d, J = 16.0 Hz, 1H), 1.08 (s, 3H), 0.96 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 194.6, 160.2, 157.6, 152.0, 149.3, 141.8, 138.1, 131.8, 128.6, 127.9, 124.0, 122.8, 116.7, 113.5, 111.0, 102.1, 54.9, 50.1, 33.4, 32.1, 29.0, 26.5. Anal. Calcd. for $C_{25}H_{23}NO_4$: C, 74.79; H, 5.77; N, 3.49. Found: C, 74.85; H, 5.59; N, 3.66.

10,11-Dihydro-7-(3,4,5-trimethoxyphenyl)-10,10-dimethyl-7H-chromeno[4,3-b]quinoline-6,8(9H,12H)-dione **(5e)** Pale-yellow powder (0.32 g, 69%). Mp (°C): 302–303.[36] IR (KBr) 3522, 3208, 1678, 1631, 1505, 1479, 1363, 1191, 1113, 1010, 764. ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 9.71 (s, NH), 8.28 (d, J = 8.0 Hz,

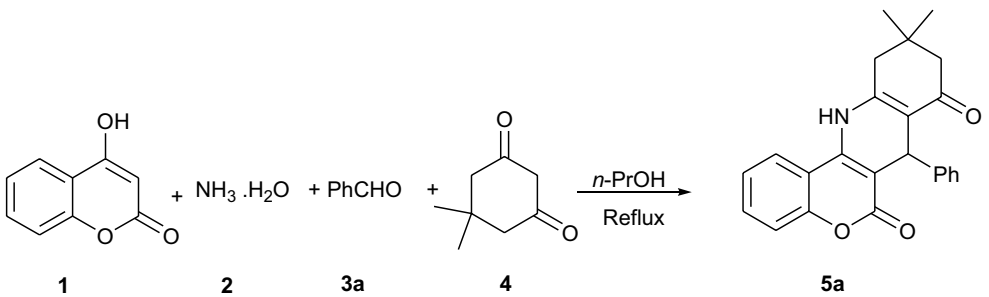
1H), 7.63 (t, J = 8.5 Hz, 1H), 7.43 (t, J = 8.0 Hz, 1H), 7.36 (d, J = 8.5 Hz, 1H), 6.53 (s, 2H), 4.94 (s, 1H), 3.68 (s, 6H), 3.59 (s, 3H), 2.71 (d, J = 16.5 Hz, 1H), 2.68 (d, J = 16.5 Hz, 1H), 2.30 (d, J = 16.0 Hz, 1H), 2.13 (d, J = 16.0 Hz, 1H), 1.11 (s, 3H), 0.97 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 194.6, 160.3, 152.4, 151.9, 149.9, 141.8, 141.1, 131.8, 124.0, 122.8, 116.8, 116.6, 113.0, 110.3, 105.2, 101.7, 59.8, 55.6, 50.1, 34.2, 32.0, 29.1, 26.4. Anal. Calcd. for $C_{27}H_{27}NO_6$: C, 70.27; H, 5.90; N, 3.03. Found: C, 70.09; H, 5.77; N, 2.85.

10,11-Dihydro-10,10-dimethyl-7-p-tolyl-7H-chromeno [4,3-b]quinoline-6,8(9H,12H)-dione **(5f)** Pale-yellow powder (0.27 g, 71%). Mp (°C): 331–333.[36] IR (KBr): 3215, 1644, 1509, 1471, 1364, 1195, 1043, 844, 762. ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 9.63 (s, NH), 8.29 (d, J = 8.0 Hz, 1H), 7.63 (t, J = 7.5 Hz, 1H), 7.43 (t, J = 8.0 Hz, 1H), 7.36 (d, J = 7.5 Hz, 1H), 7.12 (d, J = 8.0 Hz, 2H), 6.99 (d, J = 8.0 Hz, 2H), 4.91 (s, 1H), 2.65 (s, 2H), 2.25 (d, J = 16.0 Hz, 1H), 2.19 (s, 3H), 2.08 (d, J = 16.0 Hz, 1H), 1.07 (s, 3H), 0.95 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 194.5, 160.1, 151.9, 149.3, 142.8, 141.8, 135.1, 131.8, 128.4, 127.5, 123.7, 122.8, 116.7, 113.0, 110.9, 101.9, 50.1, 33.9, 32.0, 28.9, 26.5, 20.4. Anal. Calcd. for $C_{25}H_{23}NO_3$: C, 77.90; H, 6.01; N, 3.63. Found: C, 77.78; H, 5.85; N, 3.57.

7-(4-Fluorophenyl)-10,11-dihydro-10,10-dimethyl-7H-chromeno[4,3-b]quinoline-6,8(9H,12H)-dione **(5g)** Pale-yellow powder (0.30 g, 77%). Mp (°C): 218–220.[36] IR (KBr) 3470, 3301, 1711, 1631, 1593, 1470, 1360, 1194, 1148, 1041, 850, 743. ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 9.71 (s, NH), 8.31 (d, J = 7.0 Hz, 1H), 7.63 (t, J = 7.5 Hz, 1H), 7.43 (t, J = 7.0 Hz, 1H), 7.38 (d, J = 7.5 Hz, 1H), 7.25-7.23 (m, 2H), 7.04-7.01 (m, 2H), 4.95 (s, 1H), 2.66 (s, 2H), 2.26 (d, J = 16.0 Hz, 1H), 2.09 (d, J = 16.0 Hz, 1H), 1.06 (s, 3H), 0.94 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 194.6, 161.6 (d, J = 178 Hz), 152.0, 149.6, 142.1, 142.0, 132.0, 129.5, 124.1, 123.9, 123.0 (d, J = 8 Hz), 116.7 (d, J = 33 Hz), 114.6, 113.0, 110.7, 101.6, 50.0, 33.9, 32.1, 29.0, 26.6. Anal. Calcd. for $C_{24}H_{20}FNO_3$: C, 74.02; H, 5.18; N, 3.60. Found: C, 73.88; H, 5.02; N, 3.49.

7-(2-Chlorophenyl)-10,11-dihydro-10,10-dimethyl-7H-chromeno[4,3-b]quinoline-6,8(9H,12H)-dione **(5h)** Pale-yellow powder (0.30 g, 74%). Mp (°C): 299–301.[36] IR (KBr) 3289, 3079, 1707, 1631, 1605, 1508, 1472, 1362, 1197, 1147, 1021, 735. ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 9.65 (s, NH), 8.30 (d, J = 7.5 Hz, 1H), 7.62 (t, J = 7.5 Hz, 1H), 7.43 (t, J = 7.5 Hz, 1H), 7.38 (d, J = 7.5 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.18 (t, J = 7.5 Hz, 1H), 7.11 (t, J = 8.0 Hz, 1H), 5.28 (s, 1H), 2.63 (s, 2H), 2.23 (d, J = 16.0 Hz, 1H), 2.02 (d, J = 16.0 Hz, 1H), 1.07 (s, 3H), 0.94 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 194.2, 159.7, 152.0, 149.8, 142.5, 132.0, 129.2, 127.6, 126.4, 124.0, 123.7, 123.0, 122.9, 116.8, 116.6, 112.7, 110.1, 100.9, 50.1, 34.1, 31.8, 29.0, 26.3. Anal. Calcd. for $C_{24}H_{20}ClNO_3$: C, 71.02; H, 4.97; N, 3.45. Found: C, 70.86; H, 5.11; N, 3.29.

10,11-Dihydro-10,10-dimethyl-7-(2-nitrophenyl)-7H-chromeno[4,3-b]quinoline-6,8(9H,12H)-dione **(5i)** Pale-yellow powder (0.31 g, 75%). Mp (°C): 262–263.[36] IR (KBr) 3301, 1700, 1611, 1515, 1475, 1350, 1244, 1196, 1150, 1024, 739. ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 9.67 (s, NH), 8.32 (d, J = 7.5 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.65 (t, J = 7.5 Hz, 1H), 7.54 (t, J = 7.5 Hz, 1H), 7.46-7.40 (m, 2H), 7.39 (d, J = 8.0 Hz, 1H), 7.18 (t, J = 7.5 Hz, 1H), 5.85 (s, 1H), 2.64 (s, 2H), 2.22 (d, J = 16.0 Hz, 1H), 2.02 (d, J = 16.0 Hz, 1H), 1.06 (s, 3H), 0.90 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 194.4, 160.4, 151.8, 150.5, 147.8, 146.5, 142.0, 133.8, 132.0, 129.2, 124.0, 123.0, 122.1, 121.3, 116.7, 112.8, 110.0, 100.9, 49.8, 35.0, 31.9, 28.6, 26.5. Anal. Calcd. for $C_{24}H_{20}N_2O_5$: C, 69.22; H, 4.84; N, 6.73. Found: C, 69.07; H, 4.98; N, 6.57.



Scheme 1 Four-component synthesis of chromeno[4,3-*b*]quinolines

Table 1 Optimization of the reaction in different conditions (Scheme 1)

Entry	Solvent	Temp. (°C)	Yield (%)[a]
1	MeOH	Reflux	32
2	EtOH	Reflux	51
3	*n*-PrOH	Reflux	76
4	*t*-BuOH	Reflux	49
5[b]	–	120 °C	Trace
6	*n*-PrOH	r.t.	28
7[c]	*n*-PrOH	Reflux	55
8[d]	*n*-PrOH	Reflux	49
9[e]	*n*-PrOH	Reflux	36

The reactions were carried out in 5 mL solvent with **1** (1 mmol), **2** (5 mmol) **3a** (1 mmol) and **4** (1 mmol) under reflux for 12 h

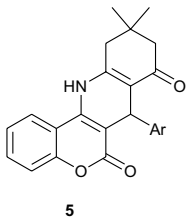
[a] Isolated yields, [b] solvent-free condition was examined, [c] 10 mmol aqueous ammonia was used, [d] 15 mmol aqueous ammonia was used, and [e] ammonium acetate (5 mmol) was used

10,11-Dihydro-10,10-dimethyl-7-(3-nitrophenyl)-7H-chromeno[4,3-b]quinoline-6,8(9H,12H)-dione **(5j)** Pale-yellow powder (0.33 g, 79%). Mp (°C): 280–282.[36] IR (KBr) 3215, 1647, 1603, 1510, 1469, 1347, 1189, 1044, 715. ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 9.82 (s, NH), 8.33 (d, J = 8.0 Hz, 1H), 8.07 (s, 1H), 8.00 (d, J = 7.5 Hz, 1H), 7.73 (d, J = 7.5 Hz, 1H), 7.65 (t, J = 7.5 Hz, 1H), 7.54 (t, J = 7.5 Hz, 1H), 7.46 (t, J = 7.5 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 5.08 (s, 1H), 2.51 (s, 2H), 2.29 (d, J = 16.0 Hz, 1H), 2.10 (d, J = 16.0 Hz, 1H), 1.10 (s, 3H), 0.96 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 194.5, 160.1, 152.1, 150.3, 147.6, 147.5, 142.5, 134.5, 132.1, 129.5, 124.1, 123.0, 122.1, 121.3, 116.7, 112.8, 110.0, 100.9, 49.9, 34.9, 32.1, 28.9, 26.4. Anal. Calcd. for $C_{24}H_{20}N_2O_5$: C, 69.22; H, 4.84; N, 6.73. Found: C, 69.46; H, 4.68; N, 6.58.

Results and discussions

In the initial study, we examined the model reaction of 4-hydroxy coumarin **1** (1 mmol), aqueous ammonia **2** (5 mmol), benzaldehyde **3a** (1 mmol) and dimedone **4** (1 mmol) in different solvents and various amounts of ammonia. The results are summarized in Table 1. It was showed that the best yield of the product **5a** was obtained in refluxing *n*-propanol (Table 1, entries 1–4). Solvent-free condition led to the trace amounts of the product (Table 1, entry 5). To examine the effect of the amount of ammonia, the reaction was carried out by employing 10 and 15 mmol of aqueous ammonia. It was observed that raising the amount of ammonia to twofold–threefold didn't improve the yield of the desired product (Table 1, entries 7–8). This implied that further increase in the amount of ammonia has no positive effect on the yield. By employing ammonium acetate as a nitrogen source, the desired product was obtained in lower yields (Table 1, entry 9).

Table 2 Synthesis of chromenoquinolines using various aldehyde derivatives



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Compound	Ar	Yield (%)[a]
5a	C_6H_5	76
5b	3-HOC_6H_4	70
5c	2-$MeOC_6H_4$	68
5d	4-$MeOC_6H_4$	72
5e	3,4,5-*tri*$MeOC_6H_2$	69
5f	4-MeC_6H_4	71
5g	4-FC_6H_4	77
5h	2-ClC_6H_4	74
5i	2-$O_2NC_6H_4$	75
5j	3-$O_2NC_6H_4$	79

[a] Isolated yields

To survey the generality of the reaction, various aromatic aldehydes were reacted under the optimized reaction condition, affording the desired products **5a–j** in moderate to good yields. Both electron-donating and electron-withdrawing aldehydes were found suitable for this reaction. The structure of cyclized compounds were confirmed by IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy. The distinguished peak related to H-4 was appeared at 4.90–5.85 ppm region as a singlet peak. Electron-withdrawing group led to the appearance of this peak at lower fields (Table 2).

Conclusion

To conclude, by the one-pot reaction of dimedone, ammonia, 4-hydroxy coumarin and aromatic aldehydes, the corresponding chromeno[4,3-*b*]quinoline was synthesized in moderate to good yields. This procedure can be applied to the synthesis of various 10,11-dihydro-10,10-dimethyl-7*H*-chromeno[4,3-*b*]quinoline-6,8(9*H*,12*H*)-diones by employing readily available starting material in a straightforward one-pot manner.

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