The First Regiospecific Synthesis of 8,8-Dimethyl-2*H*,8*H*-pyrano[2,3-*h*]quinolin-2-one and Related Compounds

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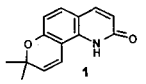
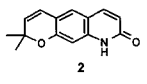
The title compound was synthesized in eight steps, starting from 6-acetamido-2,2-dimethyl-2*H*-1-benzopyran-4-one (**6**). The key steps involved are the regiospecific nitration of **6** and palladium(0)-catalyzed arylation of acrylic acid in aqueous media.

Of the several possible pyranoquinolin-2-one isomers, the angular isomer **1** and the linear isomer **2** are unknown so far. Stimulated by the antithrombotic and antiallergic properties of pyranoquinolin-2-one derivatives,[1] we desired to seek methods for the formation of these two isomers and their analogs. We wish to describe here a highly regiospecific synthesis of the two types of heterocycle **3** and **4**, which has led to the preparation of **1** and **2**.



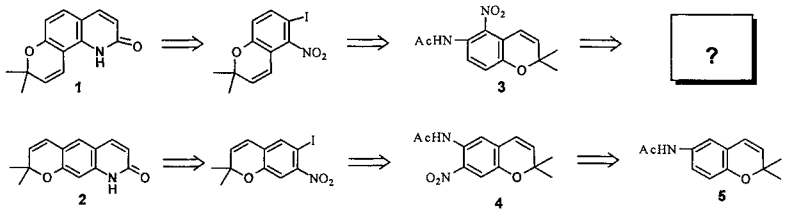
1



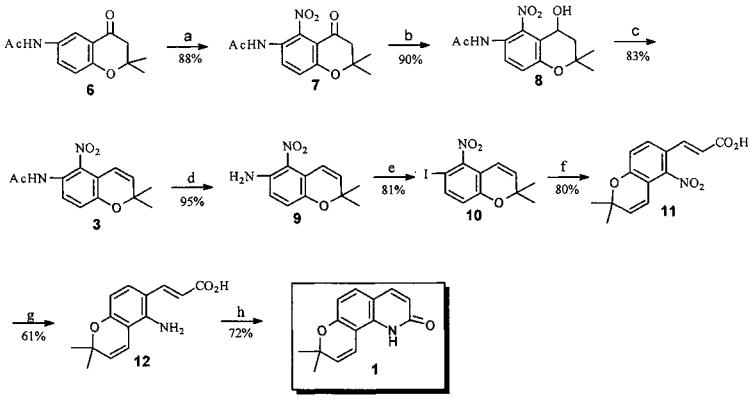
2

Retrosynthetic analysis of **1** and **2** suggested that the chromene derivatives **3** and **4** would be valuable precursors (Scheme 1). Compound **4** had been previously prepared by the nitration of 6-acetamido-2,2-dimethyl-2*H*-1-benzopyran (**5**).[2] Interestingly, nitration of **5** gave only the 7-nitro compound **4**, and the other possible isomer, the 5-nitro compound **3**, was not detectable.[2] To the best of our knowledge, the 5-nitro compound **3** has not been reported to date. It appeared therefore of interest to develop a regiospecific approach towards **3** in order to synthesize the target molecule **1**. In addition, compound **3** can be utilized for the synthesis of a variety of naturally occurring dimethylchromenes.

The present synthetic approach to **3** is based on our observation that the nitration of 6-acetamido-2,2-dimethyl-2*H*-1-benzopyran-4-one (**6**), which could be readily prepared in reasonable yield according to the published procedures,[3] gave only the 5-nitro compound **7** in 88% yield (Scheme 2). Surprisingly, the competing orientation effect of acetylamino of compounds **5** and **6** is so different and specific. This fact led to a regiospecific synthesis of **3**. Reduction of **7** with sodium borohydride in MeOH followed by dehydration of the chromanol **8** then furnished the key intermediate **3** in 81% yield for the two steps. The two isomers **3** and **4** were easily distinguished on the basis of aryl protons in the ^{1}H NMR spectra. The aryl protons of compound **3** displayed two series of double signals (J = 9.0 Hz), whereas the aryl protons of isomer **4** appeared as two singlet signals.



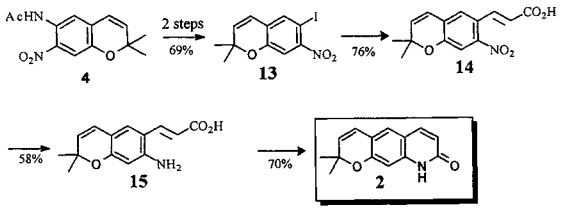
Scheme 1



(a) HNO_3, AcOH; (b) $NaBH_4$, MeOH; (c) TsOH, Benzene; (d) 5 N HCl, EtOH; (e) i) H_2SO_4 aq., $NaNO_2$; ii) KI; (f) acrylic acid, $Pd(OAc)_2$, PPh_3, K_2CO_3, DMF-H_2O; (g) $SnCl_2.2H_2O$, acetone; (h) 4% HCl

Scheme 2

Deprotection of **3** with 5 N HCl gave the 6-amino-5-nitrochromene **(9)**, which was then converted to the 6-iodo-7-nitrochromene **(10)** by reaction of the diazonium salt of **9** with KI. Palladium-catalyzed coupling of **10** with acrylic acid in aqueous DMF containing excess K_2CO_3 at 100 °C[4] afforded nitrocinnamic acid **11** in 80 % yield. While the ferrous sulfate/ammonium hydroxide reduction has been applied frequently in the conversion of *o*-nitrocinnamic acids to *o*-aminocinnamic acids, experimental details are complex and the isolated yield of *o*-aminocinnamic acids are very low.[5,6] To circumvent the low yield, we employed $SnCl_2 \cdot 2H_2O$ as a reducing agent so as to obtain an acceptable result. Reduction of **11** with $SnCl_2 \cdot 2H_2O$ in acetone gave aminocinnamic acid **12** in 61 % yield. Cyclization of **12** to **1** was accomplished by heating at reflux in 4 % HCl.[5] In the same way, compound **2** was prepared in 21 % overall yield, starting from **4** (Scheme 3).



Scheme 3

In summary, we have synthesized regiospecifically [2,3-*h*] and [1,2-*b*] fused pyranoquinolone heterocycles. This was based on the regiospecific nitration of chromanone **6** and chromene **5**, and on the palladium(0)-catalyzed arylation of acrylic acid. The availability of the two novel types of pyranoquinolone heterocycles should assist in the further development of pyranoquinolone derivatives as a biologically important class of compounds.

Solvents were purified by standard methods and dried if necessary. Reagents used were of commercial quality. Petroleum ether used had bp 60–90 °C. Melting points were performed in open capillaries and are uncorrected. NMR spectra were recorded on a 300 MHz spectrometer with TMS as internal standard. IR spectra were recorded on a Perkin-Elmer 983 spectrometer. Mass spectra were obtained using EI ionization at 70 eV.

6-Acetamido-2,2-dimethyl-2*H*-1-benzopyran-4-one (6):
Chromanone **6** was prepared according to the literature method;[3] mp 162–164 °C.

IR (KBr): ν = 3300, 2960, 1690, 1660, 1600, 1490, 720 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.40 (6 H, s, 2 CH_3), 2.10 (3 H, s, CH_3CO), 2.74 (2 H, s, H-3), 6.90 (1 H, d, J = 9.0 Hz, H-8), 7.76 (1 H, dd, J = 1.7, 9.0 Hz, H-7), 8.05 (1 H, d, J = 1.7 Hz, H-5), 9.30 (1 H, br, NH).

MS: m/z (%) = 233 (M^+, 18), 135 (100).

6-Acetamido-2,2-dimethyl-5-nitro-2*H*-1-benzopyran-4-one (7):
To a stirred solution of **6** (11.4 g, 0.049 mol) in glacial HOAc (200 mL) at 0 °C was added dropwise a solution of fuming HNO_3 (5.88 mL, 0.061 mol) in glacial HOAc. After stirring for an additional 45 min at 0 °C, the solution was poured onto ice, and the precipitate was collected (12.0 g, 88 %). Recrystallization of a small portion from EtOH gave **7** as pale yellow needles; mp 199–201 °C.

IR (KBr): ν = 3220, 2990, 1695, 1660, 1550 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.49 (6 H, s, 2 CH_3), 2.16 (3 H, s, $COCH_3$), 2.78 (2 H, s, H-3), 7.09 (1 H, d, J = 9.2 Hz, H-7), 7.59 (1 H, br, NH), 8.07 (1 H, d, J = 9.2 Hz, H-8).

Anal. Calcd for $C_{13}H_{14}N_2O_5$: C, 56.11, H, 5.07, N, 10.07; Found: C, 56.01, H, 5.11, N, 9.99.

6-Acetamido-3,4-dihydro-2,2-dimethyl-5-nitro-2*H*-1-benzopyran-4-ol (8):
$NaBH_4$ (1.6 g, 0.042 mol) was added to a stirred suspension of **7** (10.7 g, 0.038 mol) in MeOH (100 mL) at 0 °C and the mixture was stirred at this temperature for 30 min. After stirring for an additional 24 h at r.t., 2 M HCl was added and the product was extracted into EtOAc. The extract was dried ($MgSO_4$) and evaporated under reduced pressure and the residue was chromatographed on silica gel eluting with EtOAc/petroleum ether (1:1) to give **8** (9.6 g, 90 %) as a yellow solid; mp 175–177 °C.

IR (KBr): ν = 3301, 2954, 1674, 1582, 1533, 1482, 1373 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.35 (3 H, s, CH_3), 1.48 (3 H, s, CH_3), 2.05 (2 H, m, H-3), 2.17 (3 H, s, $COCH_3$), 2.60 (1 H, br, OH), 5.14 (1 H, m, H-4), 6.99 (1 H, d, J = 8.8 Hz, H-7), 7.83 (1 H, d, J = 8.8 Hz, H-8), 8.06 (1 H, br, NH).

MS: m/z (%) = 280 (M^+, 46), 238 (51), 205 (48), 164 (62).

Anal. Calcd for $C_{13}H_{16}N_2O_5$: C, 55.71, H, 5.75, N, 9.99; Found: C, 55.71, H, 5.84, N, 10.08.

6-Acetamido-2,2-dimethyl-5-nitro-2*H*-1-benzopyran (3):
A mixture of **8** (11.1 g, 0.040 mol) and TsOH (0.75 g, 0.004 mol) in toluene (120 mL) was refluxed under N_2 for 10 h until the dehydration was complete. The mixture was then cooled, filtered, and evaporated. The residue was chromatographed on silica gel eluting with EtOAc/petroleum ether (1:4) to give **3** (8.61 g, 83 %) as a yellow solid; mp 146–147 °C.

^1H NMR ($CDCl_3$): δ = 1.48 (6 H, s, 2 CH_3), 2.18 (3 H, s, $COCH_3$), 5.85 (1 H, d, J = 10.2 Hz, H-3), 6.42 (1 H, d, J = 10.2 Hz, H-4), 6.99 (1 H, d, J = 9.0 Hz, H-7), 7.87 (1 H, d, J = 9.0 Hz, H-8), 8.30 (1 H, br, NH).

MS: m/z (%) = 262 (M^+, 59).

Calcd for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N; 10.86. Found: C, 59.43; H, 5.27; N; 10.60.

6-Amino-2,2-dimethyl-5-nitro-2*H*-1-benzopyran (9):
A solution of **3** (16.2 g, 0.062 mol) in EtOH (180 mL) was refluxed with 5 N HCl for 6 h. The red solution was cooled and poured into H_2O, and the red crystals that precipitated were filtered; yield: 13.6 g (95 %). Recrystallization of a small portion from EtOH gave **9** as red needles; mp 90–92 °C.

IR (KBr): ν = 3485, 3368, 2965, 1617, 1505, 1332 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.41 (6 H, s, 2 CH_3), 5.00 (2 H, br, NH_2), 5.74 (1 H, d, J = 9.9 Hz, H-3), 6.62 (1 H, d, J = 8.7 Hz, H-7), 6.71 (1 H, d, J = 9.9 Hz, H-4), 6.89 (1 H, d, J = 8.7 Hz, H-8).

MS: m/z (%) = 220 (M^+, 36), 205 (100).

Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H; 5.49; N; 12.72. Found: C, 59.88; H; 5.41; N, 12.70.

2,2-Dimethyl-6-iodo-5-nitro-2*H*-1-benzopyran (10):
The nitroamine **9** (5.6 g, 0.025 mol) was dissolved in a mixture of H_2SO_4 (45 mL) and H_2O (110 mL) with warming, then cooled to 0 °C, and treated dropwise with stirring with a solution of $NaNO_2$ (1.93 g, 0.028 mol) in H_2O (10 mL). The mixture was stirred for an additional 1 h at 0 °C, and then addition of a solution of KI (5.8 g, 0.035 mol) in H_2O (20 mL) followed. The mixture was stirred overnight at r.t. Extraction with Et_2O gave a red gum, which was chromatographed on silica gel eluting with petroleum ether to give **10** (6.7 g, 81 %) as a yellow oil.

IR (KBr): ν = 2980, 1637, 1593, 1536, 1357, 1293, 1280 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.45 (6 H, s, 2 CH_3), 5.78 (1 H, d, J = 10.1 Hz, H-3), 6.19 (1 H, d, J = 10.1 Hz, H-4), 6.68 (1 H, d, J = 8.7 Hz, H-7), 7.56 (1 H, d, J = 8.7 Hz, H-8).

MS: m/z (%) = 331 (M^+, 26), 316 (100), 143 (49).

3-[2,2-Dimethyl-5-nitro-2*H*-1-benzopyran-6-yl]acrylic Acid (11):
A mixture of **10** (1.02 g, 3.08 mmol), $Pd(OAc)_2$ (20 mg, 0.089 mmol), PPh_3 (46 mg, 0.18 mmol), K_2CO_3 (2.12 g, 15.4 mmol), acrylic acid (0.4 g, 5.6 mmol), DMF (10 mL) and H_2O (2 mL) was heated under N_2 at 100 °C for 12 h, and then cooled, diluted with H_2O (20 mL), and extracted with Et_2O. Acidification of the aqueous layer gave a yellow solid, which was chromatographed on silica gel eluting with petroleum ether/EtOAc (3:1) to give **11** (0.68 g, 80%) as a yellow solid; mp 210–212 °C.

IR (KBr): ν = 2500–3200, 1693, 1628, 1604, 1565, 1531, 1478, 1365, 1295, 1275, 1203, 1120, 811 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.48 (6H, s, 2 CH_3), 5.83 (1H, d, J = 10.1 Hz, H-3′), 6.25 (1H, d, J = 10.1 Hz, H-4′), 6.35 (1H, d, J = 15.7 Hz, H-3), 6.93 (1H, d, J = 8.6 Hz, H-7′), 7.47 (1H, d, J = 8.6 Hz, H-8′), 7.58 (1H, d, J = 15.7 Hz, H-2), 12.59 (1H, br, CO_2H).

MS: m/z (%) = 275 (M^+, 23), 260 (92), 214 (100), 169 (32).

Anal. Calcd for $C_{14}H_{13}NO_5$: C, 61.09; H, 4.76; N, 5.09. Found: C, 61.13; H, 4.79; N, 4.96.

3-[5-Amino-2,2-dimethyl-2*H*-1-benzopyran-6-yl]acrylic Acid (12):
A solution of **11** (5.0 g, 0.018 mol) and $SnCl_2 \cdot 2H_2O$ (16.7 g, 0.072 mol) in acetone (150 mL) was refluxed for 6 h. After evaporation of solvent, the residue was basified with 28% aq ammonia (50 mL), and filtered through a layer of Celite. The precipitate was washed with H_2O (100 mL) and the combined filtrate was acidified to pH 5 with concentrated HCl to give a light brown solid. The crude product was purified by reprecipitation from aqueous ammonia to give **12** (2.72 g, 61%) as a golden yellow crystalline solid; mp 178–179 °C.

IR (KBr): ν = 3467, 3393, 2972, 1667, 1608, 1581, 1478, 1202 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 1.35 (6H, s, 2 CH_3), 5.58 (1H, d, J = 9.6 Hz, H-3′), 6.05 (1H, d, J = 9.6 Hz, H-4′), 6.10 (1H, d, J = 15.5 Hz, H-3), 6.80 (1H, d, J = 8.8 Hz, H-8′), 7.20 (1H, d, J = 8.8 Hz, H-7′), 7.77 (1H, d, J = 15.5 Hz, H-2).

MS: m/z (%) = 245 (M^+, 46), 230 (100), 212 (35), 186 (44).

Anal. Calcd for $C_{14}H_{15}NO_3 \cdot 0.25H_2O$: C, 67.32; H, 6.25; N, 5.61. Found: C, 67.37; H, 6.03; N, 5.36.

8,8-Dimethyl-2*H*,8*H*-pyrano[2,3-*h*]quinolin-2-one (1):
A mixture of **12** (0.7 g, 2.86 mmol) and 4% aq HCl (30 mL) was refluxed for 1.5 h. Cooling and filtration gave a crude product, which was purified by chromatography on silica gel eluting with EtOAc/petroleum ether (1:2) to give **1** (0.47 g, 72%) as a white solid; mp 244–245 °C.

IR (KBr): ν = 3160, 3050, 1643, 1604, 1555, 1258, 1198, 1123 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 1.40 (6H, s, 2 CH_3), 5.78 (1H, d, J = 10.1 Hz, H-9), 6.32 (1H, d, J = 9.5 Hz, H-4), 6.65 (1H, d, J = 8.5 Hz, H-6), 7.21 (1H, d, J = 10.1 Hz, H-10), 7.45 (1H, d, J = 8.5 Hz, H-5), 7.81 (1H, d, J = 9.5 Hz, H-3), 11.29 (1H, br, NH).

MS: m/z (%) = 227 (M^+, 24), 212 (100), 184 (6).

Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.80; H, 5.54; N, 6.12.

2,2-Dimethyl-6-iodo-7-nitro-2*H*-1-benzopyran (13):
Compound **13**[7] was prepared from **4**[2] following the procedure described for **10**, to give **13** (2 steps, 76%) as a yellow oil.

IR (KBr): ν = 3095, 2979, 2104, 1640, 1564, 1525, 1473, 1355, 1337, 889 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.45 (6H, s, 2 CH_3), 5.82 (1H, d, J = 10 Hz, H-3), 6.28 (1H, d, J = 10 Hz, H-4), 7.32 (1H, s, H-8), 7.57 (1H, s, H-5).

MS: m/z (%) = 331 (M^+, 32), 316 (100), 270 (19), 143 (64).

3-[2,2-Dimethyl-7-nitro-2*H*-1-benzopyran-6-yl]acrylic Acid (14):
Compound **14** was prepared from **13** following the procedure described for **11**, to give **14** (87%) as a yellow solid; mp 225–227 °C.

IR (KBr): ν = 2500–3200, 1693, 1629, 1604, 1570, 1516, 1484, 1412, 1336, 1281, 1262, 1216, 1196, 977, 765 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 1.42 (6H, s, 2 CH_3), 6.03 (1H, d, J = 9.9 Hz, H-3′), 6.46 (1H, d, J = 15.7 Hz, H-3), 6.55 (1H, d, J = 9.9 Hz, H-4′) 7.37 (1H, s, H-8′), 7.72 (1H, s, H-5′), 7.76 (1H, d, J = 15.7 Hz, H-2), 12.60 (1H, br, CO_2H).

MS: m/z (%) = 275 (M^+, 12), 260 (100), 229 (42), 214 (47), 185 (36), 169 (47).

Anal. Calcd for $C_{14}H_{13}NO_5$: C, 61.09; H, 4.76; N, 5.09; Found: C, 61.33; H, 4.70; N, 5.06.

3-[7-Amino-2,2-dimethyl-2*H*-1-benzopyran-6-yl]acrylic Acid (15):
Compound **15** was prepared from **14** following the procedure described for **12**, to give **15** (58%) as a golden yellow crystalline solid; mp 166–168 °C.

IR (KBr): ν = 3362, 3047, 2976, 1697, 1635, 1614, 1496, 1369, 1132 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 1.33 (6H, s, 2 CH_3), 5.49 (1H, d, J = 9.8 Hz, H-3′), 6.07 (1H, s, H-8′), 6.12 (1H, d, J = 15.6 Hz, H-3), 6.28 (1H, d, J = 9.8 Hz, H-4), 7.18 (1H, s, H-5′), 7.67 (1H, d, J = 15.6 Hz, H-2).

MS: m/z (%) = 245 (M^+, 26), 230 (100), 212 (65).

Anal. Calcd for $C_{14}H_{15}NO_3 \cdot 0.25H_2O$: C, 67.32; H, 6.25; N, 5.61. Found: C, 67.35; H, 6.28; N, 5.53.

8,8-Dimethyl-2*H*,8*H*-pyrano[1,2-*b*]quinolin-2-one (2):
Compound **2** was prepared from **15** following the procedure described for **1**, to give **2** (70%) as a white solid; mp 236–238 °C.

IR (KBr): ν = 3138, 2980, 1650, 1629, 1567, 1468, 1267, 1154 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 1.40 (6H, s, H-8), 5.80 (1H, d, J = 9.9 Hz, H-7), 6.29 (1H, d, J = 9.6 Hz, H-4), 6.47 (1H, d, J = 9.9 Hz, H-6), 6.64 (1H, s, H-10), 7.32 (1H, s, H-5), 7.75 (1H, d, J = 9.6 Hz, H-3), 11.58 (1H, br, NH).

MS: m/z (%) = 227 (M^+, 19), 212 (100), 184 (5).

Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16; Found: C, 73.82; H, 5.80; N, 5.98.

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