Indian Journal of Chemistry
Vol. 43B, March 2004, pp. 624-628

Synthesis of benzofuro-4-anilino-2*H*-1-benzopyran-2-one and benzofuro-pyrano -2*H*-1-benzopyran-2-one

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Received 6 November 2002; accepted (revised) 18 June 2003

The title compounds are synthesized from the corresponding 4-hydroxy-benzopyran-2[*H*]-ones **5a,b** .2, 4-Dihydroxy-acetophenone **1a,b** on condensation with 2-bromocyclohexanone, followed by linear cyclisation and then on reaction with diethyl carbonate in presence of pulverised sodium gives 6, 7, 8, 9-tetrahydro-4-hydroxy-benzofuro [3, 2-*g*]-2*H*-1-benzopyran-2-one **5a,b**, which on reaction with aniline, followed by dehydrogenation with palladised charcoal gives benzofuro[3, 2-*g*]-4-anilino-2*H*-1-benzopyran-2-one **7a,b**. **5a,b** on condensation with benzalacetone followed by dehydrogenation with palladised charcoal furnishes 2-methyl-4-phenyl-4-hydro-pyrano[3, 2-*c*]-benzofuro[3, 2-*g*]-5*H*-benzopyran-5-one **9a,b**.

IPC: Int.Cl.[7] C 07 D 311 / 00

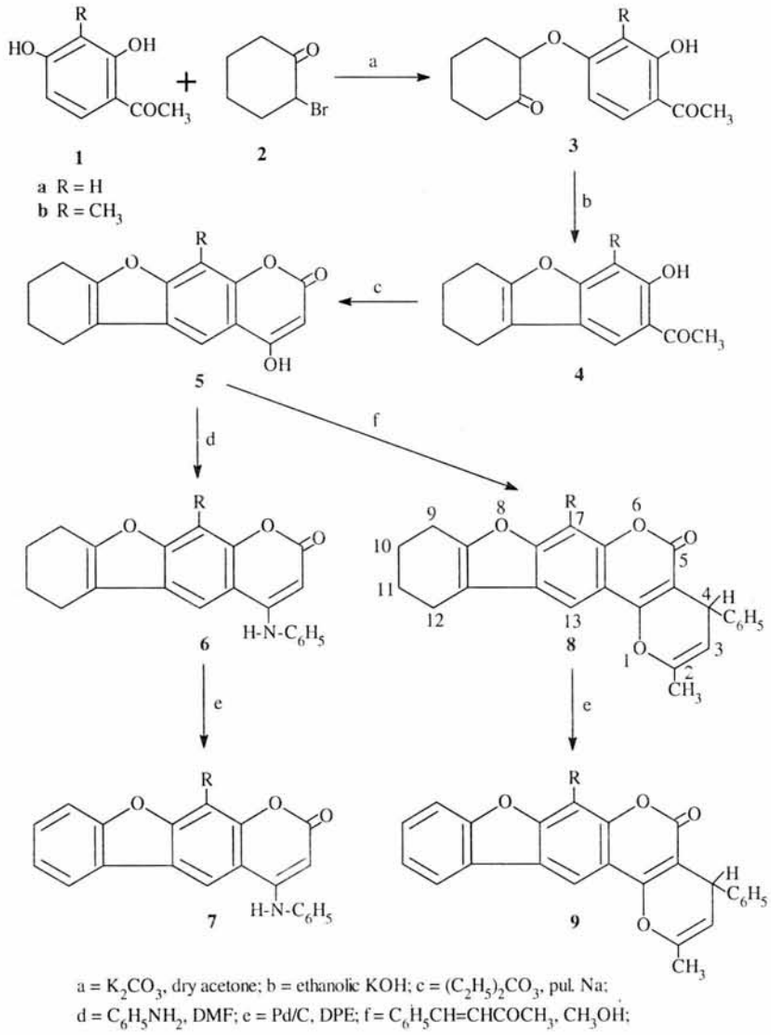
4-Hydroxycoumarin and its derivatives are known to be useful as anticoagulant drugs[1] warfarin and dicoumarol[2] are well known for their anticoagulent propeties[3] Recently 3-substituted-4-hydroxycoumarins[4] and tricoumerol[5] have found to possess some HIV inhibitory potency. Coumarins substituted at 3, 4-position show various biological activities[6, 7] This has stimulated the search for new 4-hydroxycoumarin derivatives and its convenient method of synthesis.

Bush and Trager[8] have synthesized warfarin by condensing 4-hydroxycoumarin with benzalacetone. G. Appendino *et al.*[9] have reported synthesis of various pyrano and furanocoumarins from 4-hydroxy-coumarins and acrolein. A review by Trivedi *et al.*[10] have discussed various methods of synthesis of 4-hydroxy coumarin. Herein very simple and covenient method of synthesis of various 4-aminocoumarins and benzofuro-pyranocoumarins from 4-hydroxycoumarin is reported.

2, 4-Dihydroxyacetophenone **1** on condensation with 2-bromocyclohexanone **2** in presence of anhydrous potassium carbonate and dry acetone gave 4-(cyclohexane-2-onyloxy)-2-hydroxy acetophenone **3**, which on cyclisation in presence of 0.1 *N* ethanolic KOH gave 5, 6, 7, 8-tetrahydro-2-hydroxy-3-acetyl-dibenzofuran **4**. Formation of **4** can be explained on the basis of intramolecular aldol condensation[11] Compound **4** on condensation with diethylcarbonate[12] in presence of sodium gave 6, 7, 8, 9-tetrahydro-4-hydroxy-benzofuro[3, 2-*g*]-2*H*-1-benzopyran -2 - one **5**. The structure of all these compounds were confirmed by its ^{1}H NMR and IR spectra. Compound **5a** on refluxing with aniline[13] in dimethyl formamide gave 6, 7, 8, 9-tetrahydro-4-anilino-benzofuro[3, 2-*g*]-2*H*-1-benzopyran-2-one **6a**. The ^{1}H NMR spectrum taken in DMSO-d_6, showed multiplet at 1.5-1.9 for four protons indicating two -CH_2 groups at C-7 and C-8. Another multiplet at 2.2-2.7 for four protons indicated two -CH_2 groups at C-6 and C-9. Singlet at 5.3 for one proton indicated proton at C-3. Multiplet from 6.9-7.2 for seven protons indicated all aromatic protons. Singlet at 9.3 for one proton indicated -N-H proton. The IR spectrum of this compound also showed one band for secondary amine at 3300 cm^{-1}. The dehydrogenation of **6** with palladised charcoal in refluxing diphenyl ether (DPE) gave benzofuro[3, 2-*g*]-4-anilino-2*H*-1-benzopyran-2-one **7a**. The ^{1}H NMR spectrum of this compound taken in DMSO-d_6 confirmed its structure. The disappearance of multiplet from 1.5 to 2.7 region and appearance of extra signal in aromatic region confirmed the dehydrogenation has taken place.

Similar series of reactions were carried out on 2, 4-dihydoxy-3-methylacetophenone to obtain 4-anilino-11-methyl-benzofuro[3, 2-*g*]-2*H*-1-benzopyran-2-one **7b**. The structure of all compounds were confirmed by its ^{1}H NMR, IR and mass spectra (**Scheme I**).

Compound **5b** on condensation with benzalacetone in presence of alkali gave 2, 7-dimethyl-4-hydro-4-phenyl-pyrano[3, 2-*c*]-9, 10, 11, 12-tetrahydro-benzofuro[3 2-*g*]-5*H*-benzopyran-5-one **8b**. The structure of this compound was confirmed by its ^{1}H NMR spectrum taken in DMSO-d_6 The multiplet at δ 1.5-1.9 for 4 H indicated two -CH_2 groups at



Scheme I

C-10 and C-11. Two singlets at 2.3 and 2.35 each 3H indicated two -CH_3 groups at C-2 and C-7. Multiplet at 2.6 - 2.8 for 4H indicated two -CH_2 at C-9 and C-12. Singlet at 6.0 for one proton indicated proton at C-3. Singlet at δ 6.35 indicated another proton at C-4. Multiplet at δ 7.1 - 7.6 for 6H indicated all aromatic protons. It was then dehydrogenated with palladised charcoal by refluxing in diphenyl ether to get 2, 7-dimethyl-4-hydro-4-phenyl-pyrano[3, 2-*c*]benzofuro-[3, 2-*g*]-5*H*- benzopyran -5 -one **9b**. The disappearance of multiplet from aliphatic region and appearance of signals in aromatic region in NMR confirms that the dehydrogenation has taken place. The structures of all the compounds were confirmed by its NMR, IR and mass spectra and elemental analyses. Similarly **5a** on condensation with benzalacetone in presence of alkali gave 2-methyl-4-hydro, 4-phenyl-pyrano[3, 2-*c*]-9, 10, 11, 12-tetrahydro-benzofuro-[3, 2-*g*]-5*H*-benzopyran-5-one **8a,** which on dehydrogenation with palladised charcoal in refluxing with diphenyl ether gave 2-methyl-4-hydro-4-phenyl-pyrano[3, 2-*c*]benzofuro[3, 2-*g*]-5*H*-benzopyran-5-one **9a**.

Experimental Section

Melting points are uncorrected ^{1}H NMR spectra were recorded on a Perkin-Elmer R-32, 90 MHz spectrometer using TMS as internal standard (chemical shifts in, ppm) and IR spectra in KBr on Schimadzu IR-408 spectrophotometer ($\sqrt{}_{max}$ in cm^{-1}). Silica gel (mesh size 60-120) was used for column chromatography.

4-(Cyclohexan-2-onyloxy)-2-hydroxy acetophenone 3a. A mixture of 2, 4-dihydroxyacetophenone (6.0 g 0.004 mole) 2-bromocyclohexanone (5.2 mL, 0.004 mole) and anhyd. K_2CO_3 potassium carbonate (15 g) was refluxed in dry acetone (150 mL) for 8 hr. It was then worked out by pouring in ice : water. The product obtained was purified by column chromatography using pet. ether : benzene (1 : 1) mixture as colourless crystals, yield 48%, m.p. 136°C. Anal. Found: C, 67.92; H 6.47. Calcd for $C_{14}H_{16}O_4$: C, 67.74; H 6.45%

4-(Cyclohexan-2-onyloxy)-2-hydroxy-3-methyl-acetophenone 3b. It was prepared according to the procedure described for **3a** starting from 2, 4-dihydroxy-3-methylacetophenone and crystallised from benzene yield 60%, m.p.125°C. Anal.Found: C, 69.02; H, 6.99. Calcd for $C_{15}H_{18}O_4$C 68.70; H 6.87% ^{1}H NMR: ($CDCl_3$): 2.2 (3H, s, -CH_3 at C-3) 2.55 (s, 3H, -$COCH_3$) 1.7-2.6 (8H, m, all CH_2), 4.7 (1H, t, -O-CH-CO) 6.2 (1H, d, *J*=9Hz, H at C-5), 7.45(1H, d, *J*=9 Hz, H at C-6). IR (KBr): 2500-3000, 1670, 1620, 1480, 1400, 1350, 1310, 1250, 1115, 1080, 970, 860, 790, 760 cm^{-1}.

5,6,7,8-Tetrahydro-2-hydroxy-3-acetyl dibenzofuran 4a. Compound **3a** (1.0 g 0.004 mole) was dissolved in 0.1 *N* ethanolic KOH (100 mL) and refluxed on a water bath for 8 hr. The excess ethanol was then distilled off and the contents poured into ice-HCl (1:1). The product obtained was purified by column chromatography using benzene. It crystallised from benzene. yield 60%, m.p. 182°C. Anal.Found: C, 73.50; H 6.83. Calcd for: $C_{14}H_{14}O_3$: C, 73.50, H, 6.90% ^{1}H NMR ($CDCl_3$): 1.6-2.0 (4H, m, -CH_2 at C-6 and C-7) 2.4-2.8 (4H, m, -CH_2 at C-5 and C-8) 2.6 (3H, s, -$COCH_3$), 6.9 (1H, s, H at C-1), 7.7 (1H, s, H at C-4) and 12.0 (1H, s, chelated -OH). IR (KBr): 2600-3100, 1650, 1600, 1490, 1430, 1320, 1300, 1270, 1190, 1145, 1030, 980, 930, 840 cm^{-1}

5,6,7,8-Tetrahydro-2-hydoxy-1-methyl-3-acetyl-dibenzofuran 4b. It was prepared according to the procedure described for **4a** starting from **3b**. It was crystallised from benzene. yield 68%, m.p. 148°C. Anal. Found: C 73.45; H, 6.62. Calcd for $C_{15}H_{16}O_3$: C, 73.77; H 6.56%. ^{1}H NMR ($CDCl_3$): 1.7-2.0 (4H, m, -CH_2 at C-6 and C-7) 2.45 (3H, s, CH_3 at C-1); 2.5-2.8 (4H, m, -CH_2 at C-5 and C-8); 2.7 (3H, s, -$COCH_3$); 7.5 (1H, s, H at C-4) 12.6 (1H, s, Chelated-OH). IR(KBr): 2500-3000, 1650, 1420, 1400, 1350, 1310, 1280, 1250, 1215, 1180, 1100, 1070, 980, 920, 850, 760 cm^{-1}.

6, 7, 8, 9-Tetrahydro-4-hydroxybenzofuro[3, 2-g]-2*H*-1-benzopyran-2-one 5a. Compound **4a** (1.0 g 0.004 mole) dissolved in diethyl carbonate (10.0 mL) was added to pulverised sodium (1 g) and heated on a water bath for 8 hr. Ethanol was added to decompose unreacted Na metal and the contents were poured into ice: HCl (1:1). The product was crystallised from ethanol, yield 70%, m.p. 280°C. Anal. Found: C, 70.09; H, 4.97. Calcd for $C_{15}H_{12}O_4$: C, 70.33; H, 4.69%; ^{1}H NMR (DMSO-d_6): 1.6-2.0 (4H, m, -CH_2 at C-7 and C-8), 2.4-2.8 (4H, m, -CH_2 at C-6 and C-9) 5.4(1H s H at C- 3)7.25 (1H, s, H at C-11), 7.65 (1H, s, H at C-5).

11-Methyl-4-hydroxy-6, 7, 8, 9-tetrahydrobenzofuro[3, 2-g]-2*H*-1-benzopyran-2-one 5b. It was prepared according to the procedure described for **5a** starting from **4a**. It crytallised from ethanol, yield 50%, m.p. 301°C. Anal. Found: C, 70.93; H, 4.70. Calcd. for $C_{16}H_{14}O_4$: C, 71.11; H, 5.19%; ^{1}H NMR (DMSO-d_6): 1.7-2.0 (4H, m, -CH_2 at C-7 and C-8), 2.45 (s, 3H, -CH_3 at C-11) 2.5-2.8 (4H, m, -CH_2 at C-6 and C-9) 5.45 (1H, s, H at C-3), 7.7 (1H, s, H at C-5); IR (KBr): 3200-3400, 2990, 2800, 1710, 1480, 1250, 1080, 910, 805, 685 cm^{-1}

6, 7, 8, 9-Tetrahydro-4-anilinobenzofuro[3, 2-g]-2*H*-1-benzopyran-2-one 6a. Compound **5a** (0.5 g, 0, 0.02 mole) and aniline[13] (2 mL) was refluxed in DMF (100 mL) for 45 min. The resulting mixture was dissolved in methanol (100 mL) and the solution was treated with aq. NaOH (0.1 *N*, 200 mL) under stirring. After 30 minutes the precipitates formed were collected and recrystallised from DMF:water (1:1), yield 77%, m.p. 326°C (decomposes). Anal. Found: C, 76.18; H, 5.32 N 3.99.Calcd for $C_{21}H_{17}O_3N$: C 76.13; H, 5.13, N, 4.23%. IR(KBr): 3300, 2956, 2800, 1710, 1595, 1485, 1250, 1070 915, 805, 685 cm^{-1} .

6, 7, 8,9-Terahydro-4-anilino-11-methylbenzofuro[3, 2-g]-2*H*-1-benzopyran-2-one 6b. It was prepared according to the procedure described for **6a** starting from **5b**. It was crystallised from DMF : water (1:1), yield 70%, m.p. 320°C. Anal.Found: C, 76.35; H, 5.82; N, 3.86. Calcd for $C_{22}H_{19}O_3N$: C, 76.52 H, 5.51, N, 4.06%; ^{1}H NMR (DMSO-d_6): 1.8-2.0 (4H, m, -CH_2 at C-7 and C-8) 2.6-2.9 (4H, m, -CH_2 at C-6 and C-9), 2.55 (3H, s, -CH_3 at C-11), 5.4 (1H, s, H at C-3) 7.2-7.6 (6H, m, all aromatic protons); 9.35 (1H, s, -N-H proton); IR (KBr): 3300, 2956, 2800, 1710, 1550, 1500, 1460, 1410, 1330, 1290, 1240, 1160, 1100, 1070, 940, 900, 840, 790, 750 cm^{-1}.

Benzofuro[3,2-*g*]-4-anilino-2*H*-1-benzopyran-2-one 7a. Compound **6a** (0.25g 0.00075 mole) and palladised charcoal (0.2 g) was refluxed in diphenyl ether (10 mL) for 8hr. It was filtered and diphenyl ether was removed by steam distillation. The product was crystallised from DMF. yield 62%, m.p. above 350°C. Anal. Found: C, 77.25; H, 4.20, N, 3.97. Calcd. for $C_{21}H_{13}O_3N$: C, 77.06; H, 3.98, N, 4.28%; ^{1}H NMR (DMSO-d_6): 5.4 (1H, s, H at C-3), 6.9-7.4 (11H, m, all aromatic protons) 9.3(1H, s, -N-H proton); IR(KBr): 3300, 2960, 2810, 1720, 1560, 1500, 1460, 1400, 1340, 1280, 1240, 1150, 1100, 1070, 940, 900, 860, 800 750 cm^{-1}; Mass: m/z (M^+) 327.

Benzofuro[3,2-*g*]-4-anilino-11-methyl-2*H*-1-benzopyran-2-one 7b. It was prepared according to the procedure described for **7a** starting from **6b**, yield 65%, m.p. above 350°C. Anal.Found: C 77.35, H, 4.53; N, 3.99. Calcd for $C_{22}H_{15}O_3N$: C, 77.42; H, 4.40; N 4.11%; ^{1}H NMR (DMSO-d_6): 2.4 (3H, s, CH_3 at C-11), 5.4 (1H, s, H at C-3), 6.9-7.45 (10H, m, all aromatic protons) 9.35 (1H, s, -N-H proton); IR (KBr): 3300, 2950, 2830, 1715, 1560, 1500, 1460, 1390, 1350, 1290, 1220, 1160, 1090, 1010, 950, 900, 850, 790, 730 cm^{-1}; Mass: m/z (M^+) 341.

2-Methyl-4-hydro-4-phenylpyrano[3, 2-*c*]-9, 10, 11, 12-tetrahydrobenzofuro [3, 2-*g*]-5*H*-benzopyran-5-one 8a. A mixture of **5a** (1 g, 0.004 mole), benzalacetone (1 g) was stirred at reflux temperature for 20 hr in methanol (50 mL) The reaction was monitored by TLC. The solvent was removed under reduced pressure and acidified with concentrated HCl (5*N*). The mixture was extracted with ether (3 × 100 ml) by using saturated solution of NaCl (30 mL). The ether was evaporated to obtain product **8a**. It was crystallised from ethanol.yield 73%, m.p. 135°C. Anal. Found: C, 77.93; H, 5.02. Calcd for $C_{25}H_{20}O_4$: C, 78.12; H, 5.21%; ^{1}H NMR (DMSO-d_6):1.5- 1.9 (m, 4H, -CH_2 at C-10 and C-11) 2.3 (s, 3H, -CH_3 at C-2) 2.6-2.8 (m, 4H, -CH_2 at C-9 and C-12), 6.0 (s, 1H, H at C-3), 6.35 (s, 1H, H at C-4)7.2-7.7 (m, 7H, all aromatic protons); IR (KBr): 2959, 2800, 1710, 1600, 1530, 1495, 1440, 1365, 1260, 1140, 1075, 1035, 810, 760 cm^{-1}.

2-Methyl-4-hydro-4-phenylpyrano[3, 2-*c*]benzofuro[3, 2-*g*]-5*H*-benzopyran-5-one 9a. A mixture of **8a** (0.5 g) and palladised charcoal (0.25 g, 0.0013 mole) was refluxed in diphenyl ether (10 mL) for 8hr. It was filtered and diphenyl ether was removed by steam distillation . The product was purified by crystallisation from ethanol, yield 70%, m .p . 192°C. Anal.Found: C, 78.66; H, 3.96. Calcd for $C_{25}H_{16}O_4$: C, 78.95; H, 4.211%; ^{1}H NMR (DMSO-d_6): 2.35 (3H, s, -CH_3 at C-2), 6.05 (1H, s, H at C-3), 6.35 (1H, s, H at C-4), 7.2-7.9 (11H, m, all aromatic protons); IR(KBr): 2990, 2800, 1720, 1600, 1500, 1480, 1410, 1350, 1250, 1130, 1060, 1040, 840, 810, 750 cm^{-1}; Mass: m/z (M^+) 380.

2, 7-Dimethyl-4-hydro-4-phenyl-pyrano[3, 2-c]-9,10,11,12-tetrahydrobenzofuro [3, 2-*g*]-5*H*- benzopyran-5-one 8b. It was prepared according to the procedure described for **8a** starting from **5b,** yield 58%, m.p. 240°C. Anal.Found: C, 78.01; H, 5.28. Calcd for $C_{26}H_{22}O_4$: C, 78.39; H, 5.53%; ^{1}H NMR (DMSO-d_6): 1.5-1.9 (4H, m, -CH_2 at C-10 & C-11) 2.3 (s, 3H, -CH_3 at C-7) 2.35 (s, 3H, -CH_3 at C-2), 2.6-2.8 (4H, m, -CH_2 at C-9 and C-12), 6.05 (s, 1H, H at C-3), 6.35 (s, 1H, H at C-4) 7.2-7.8 (m, 6H, all aromatic protons); IR (KBr): 2980, 2800, 1710, 1600, 1500, 1480, 1430, 1360, 1250, 1150, 1080, 1020, 800, 750 cm^{-1}.

2,7-Dimethyl-4-hydro-4-phenylpyrano[3, 2-c]benzofuro-5*H*-benzopyran-5-one 9b. It was prepared according to the procedure described for **9a** starting from **8b**. yield 55%, m.p. 215°C. Anal.Found: C, 78.94; H 4.32. Calcd for $C_{26}H_{18}O_4$: C, 79.19; H, 4.569%; ^{1}H NMR (DMSO-d_6): 2.3 (s, 3H, -CH_3 at C-7) 2.35 (s, 3H, -CH_3 at C-2) 6.05 (s, 1H, H at C-3), 6.35 (s, 1H, H at C-4) 7.2-7.9 (m, 10H, all aromatic protons); IR(KBr): 2995, 2810, 1720, 1600, 1500, 1470, 1420, 1365, 1240, 1100, 1050, 980, 840, 800, 750 cm^{-1}; Mass: m/z (M^+) 394.

Acknowledgement

The author is thankful to Prof. A K Rakshit, Head, Chemistry Department, Faculty of Science, M.S.U. Baroda, to Dr. S. S. Madhav Rao, Chemistry Department, Faculty of Science, M.S.U. Baroda for their interest and help in this work and to the Director, Malti Chem Research Centre and Sun Pharma Research Centre for ^{1}H NMR spectra.

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