SHORT PAPER

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The synthesis of some novel substituted benzochromene derivatives†

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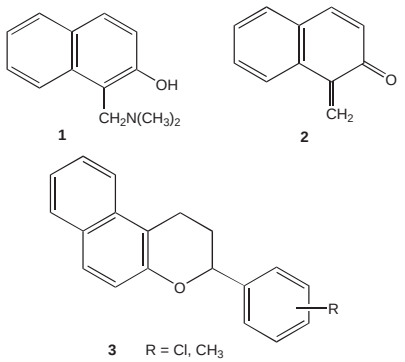
Quinonemethides generated from 6-bromo-2-[(*N*,*N*-dibenzylamino)methyl]naphthalen-1-ol (5) and 1-(*N*, *N*-dimethylaminomethyl)naphthalen-2-ol (1) react in inverse-electron-demand Diels-Alder reactions with substituted styrenes, *N*-vinylimidazole, and butyl vinyl ether, to afford the expected dihydro-benzo[*h*] and -benzo[*f*] chromenes in 36–53% yields.

Keywords: Mannich bases, benzochromenes, naphthopyrans, quinone methides

There has been considerable interest in chromenes and their benzo-derivatives, not least because of their value for a variety of industrial, biological and chemical synthetic uses.[1] A number of naturally occurring chromene derivatives are used as effective reagents against asthma, arthritis, depression, anxiety, loss of appetite, Alzheimer's and other disorders of the central nervous system.[2-4] For example, substituted 2-amino-4*H*-benzochromenes are proposed for the treatment of immune diseases (psoriasis, ulcerous colitis, chronic hepatitis, *etc*.[5]) and diabetic complications resulted from an increase in permeability of blood vessels and a change in blood pressure[5].

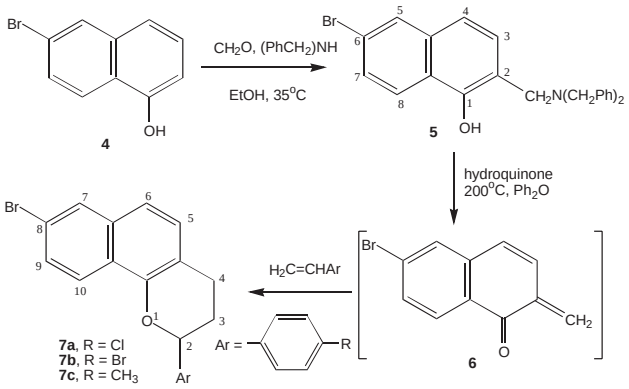
A large number of methods have developed for the synthesis of these heterocycles.[1,5-7] Brugidou and Christol[8] have synthesised benzochromene derivatives *via* the inverse electron demand Diels-Alder reaction of naphthalene quinone-methide with styrenes. 2-Chloromethyl-4,6-dimethylphenol has been transformed into chromene derivatives in the presence of base *via* an *o*-quinonemethide.[9] Similar chromene derivatives have been obtained from *o*-quinonemethides with isobutylene, styrene, and 1,1-diphenylethylene.[10] Bilgiç *et al*.,[11] Yalçınkaya *et al*.,[12] and Büyükkıdan *et al*.[13] have also synthesised derivatives of chromene and benzochromenes using substituted (Cl, CH_3) styrenes by the same method.



Recently, Yavari *et al*.[14] have reported an efficient synthetic route to polysubstituted benzochromenes using tert-butyl isocyanide and dibenzoylacetylene or dimethyl acetylene-dicarboxylate (DMAD) in the presence of a naphthol such as 1-naphthol, 2-naphthol, *etc*.

In the present work, we report the synthesis of a new Mannich base (**5**) and some novel derived benzochromene derivatives.

6-Bromo-2-[(*N*,*N*-dibenzylamino)-methyl]naphthalen-1-ol (**5**) was synthesised according to the method of Caldwell and Thompson.[15] The reaction of 6-bromo-1-naphthol **(4)** with dibenzylamine in the presence of formaldehyde at room temperature afforded the Mannich base **5** in 42 % yield (Scheme 1).



Scheme 1

The structure of **5** was established on the basis of its elemental analyses, UV, ^{1}H and ^{13}C NMR and IR spectral data. Its ^{1}H NMR spectrum showed two singlets identified as benzylic (CH_2Ph) (δ = 3.52 ppm) and $-CH_2N$ (δ = 3.95 ppm) protons. The characteristic H5 proton of compound **5** gives doublet at 7.80 ppm (J = 2 Hz.). The small splitting may be due to long-range proton coupling. The second further down field proton signals are due to the H8 which is *peri* to OH group at 7.61 ppm ($J_{8,7}$ = 9.0 Hz.). The H7 proton coupled with H8 to give doublet at 7.41 ppm ($J_{7,8}$ = 9 Hz.). The 4H and 3H give AB system at δ = 7.49 and 7.03 ($J_{3,4}$ = 8.8 Hz.), respectively as expected. The proton-decoupled ^{13}C NMR spectrum of **5** showed 16 distinct resonances in agreement with proposed structure.

The inverse electron demand Diels–Alder reaction of **5** with 4-substituted (Cl, Br, CH_3) styrenes in the presence of a small amount of hydroquinone in diphenyl ether at 200 °C gave benzo[*h*]chromene derivatives **7a**–**c** *via* the naphthoquinone methide **6** (Scheme 1). Yalçınkaya has reported[9] that the use of 2- and 3-substituted styrenes decreases the yield in the synthesis of substituted benzo[*f*]chromans (**3**) from the 2-naphthol Mannich base **1**. For this reason, we used only 4-substituted styrenes in our reactions.

The structures of 7a, 7b and 7c were determined on the basis of spectral data (^{1}H and ^{13}C NMR, IR, UV and elemental analyses) and compared with literature data.[11,12.16,17] All findings were in good agreement with the proposed structures.

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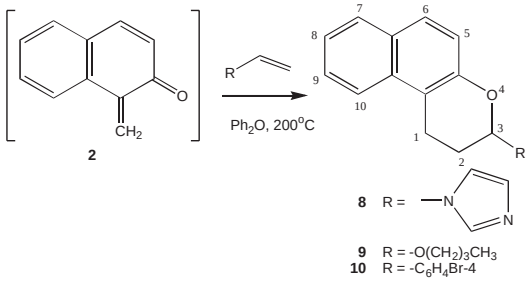
In a further study, we synthesised the 2-substituted benzo[*f*]chromenes **8–10** using 1-vinylimidazole, *n*-butyl vinyl ether and 4-bromostyrene from the 1-naphthol Mannich base **1** via the naphthoquinone methide **2** (Scheme 2).



Scheme 2

The ^{1}H NMR spectra of **8** give a singlet at 7.71 ppm for H2' of the imidazole moiety as expected. A multiplet centred at 7.68 comes from H7 and H10. The H5 and H6 gave an AB system at 7.57 and 6.98 ppm ($J_{5,6}$ = 8.9 Hz.). The H8 and H9 give two triplets at 7.31 and 7.43 ($J_{6,7}$ = 7.5 Hz.). The imidazole protons H4' and H5' gave a broad, apparent doublet, at 7.05 ppm. The characteristic methine proton (–NCHO–) give a triplet at 5.82 ppm (J = 5.75 Hz).[16, 17] The ^{13}C NMR spectrum of **8** showed 16 distinct resonances (methine carbon shift δ = 82.10 ppm) in agreement with the proposed structure.

In the ^{1}H NMR spectrum of **9**, the methine proton appears at δ = 5.19 ppm as a triplet (J = 2.86 Hz). In the ^{13}C NMR spectra of **9** the methine carbon signal at δ 97.5 ppm and the other16 resonances supported the proposed structure.

All spectral findings of **10** were in good agreement with literature data.[11, 12, 16, 17]

In summary: the novel benzochromene derivatives **7a–c** were synthesised from a new Mannich base (**5**). Three other benzochromene derivatives **8**–**10** were prepared from the known Mannich base **1**. In these reactions, dimeric products from the naphthoquinonemethides were not isolated from the crude products.

Experimental

Solvents were dried and distilled by standard procedures. The Mannich base **1** was synthesised by the literature method.[15] Melting points were measured on Electrothermal 9100 apparatus. Infrared spectra were measured on a Perkin-Elmer 1717 FT spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX 500 (125) MHz spectrometer, and reported in δ units with TMS as an internal standard. UV spectra were recorded on a PU 8720 Philips spectrometer. The elemental analyses were performed using a CHNS-932 (LECO) analyzer.

6-Bromo-2-[(N,N-dibenzylamino)methyl]naphthalen-1-ol (**5**)**:** 6-Bromo-1-naphthol (10g, 44.8 mmol) and dibenzylamine (8.83g, 44.8 mmol) in ethyl alcohol (75 ml) were stirred at 25 °C for 5 min. Formaldehyde (37%, 1.25 ml, 44.8 mmol) was added dropwise to this mixture over 1 h and the mixture was left overnight to afford a white solid. Crystallisation from ethyl alcohol gave the Mannich base **5** as white crystals (42%, m.p. 110–111 °C). ^{1}H NMR (500MHz, $CDCl_3$) δ = 7.80 (br.s, 1H, H_5), 7.61 (d, A part of AB system, $J_{7,8}$ = 9Hz. 1H, H_7), 7.49 (d, A part of AB system, $J_{3,4}$ = 8.8 Hz, 1H, H_4), 7.41 (d, B part of AB system, $J_{7,8}$ = 9 Hz, 1H, H_8), 7.25 (m, 10ArH), 7.03 (d, B part of AB system, $J_{3,4}$ = 8.8 Hz, 1H, H_3), 3.95 (s, 2H, NCH_2-), 3.52 (s, 4H, NCH_2Ph). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 158.5, 143.6, 138.4, 133.2, 132.7, 131.7, 131.4, 130.7, 130.4, 129.9, 124.8, 122.1, 117.9, 114.2, 59.9, 53.15. IR (KBr) cm^{-1}: 3692, 3678, 3651, 3569, 3063, 2889, 2802, 2362, 2343, 1655, 1648, 1543, 1465, 1331, 1294, 1212, 1193, 1151, 1030, 1003, 857, 720, 603, 426. U.V. (MeOH), λ_{max} (log ε): 240.8 (1.43). Anal: Calcd. for $C_{25}H_{22}BrNO$: C, 69.45, H, 5.12. Found: C, 69.42, H, 5.18 %.

General procedure for the synthesis of benzochromene derivatives **7a–c, 8**–**10**: Mannich base **5** or **1** and the dienophile (4-substituted styrene, 1-vinylimidazole or n-butyl vinyl ether) in a ratio of 1 : 1 were mixed in diphenyl ether (20 ml) containing hydroquinone (20 mg). The resulting mixture was heated under dry nitrogen at 200 °C for 20 h. The solvent was removed *in vacuo* and the residue (except **9**) was crystallised from ethyl acetate to give crystalline products **7a–c**, **8** and **10**. The crude product **9** was distilled at 197 °C/20 mmHg to give a pale brown liquid.

8-Bromo-2-(4-chlorophenyl)-3,4-dihydro-2H-benzo[h]chromene (**7a**): white crystals (38%), m.p. 207–208 °C. ^{1}H NMR (500MHz, $CDCl_3$) δ =7.85 (br.s, 1H, H_7), 7.61 (d, A part of AB system, $J_{9,10}$ = 8.9 Hz, 1H, H_{10}), 7.49 (d, B part of AB system, $J_{9,10}$ = 8.9 Hz, 1H, H_9), 7.47 (d, A part of AB system, $J_{3,4}$ = 8.7 Hz, 1H, H_4), 7.32 (m, 4ArH), 7.07 (d, B part of AB system, $J_{3,4}$ = 8.7 Hz, 1H, H_3), 5.02 (dd, 1H, J = 2.01 and 10.14 Hz), 3.06 (m, 2H, CH_2CH_2CH), 2.29, 2.01 (m+m, 2H, CH_2CH_2CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 153.2, 140.25, 132.0, 130.7 (2C), 130.1, 129.2 (2C), 127.9, 127.5, 126.3, 124.3, 120.7, 117.6, 114.25, 77.9, 30.1, 22.0. IR (KBr) cm^{-1}: 3053, 2951, 2920, 2873, 1612, 1587, 1443, 1413, 1190, 1154, 1016, 906, 719, 693, 637, 507, 456. U.V. (MeOH), λ_{max} (log ε): 242.4 (1.39). Anal: Calcd. for $C_{19}H_{14}BrClO$: C, 61.07, H, 3.78. Found: C, 61.04, H, 3.77 %.

8-Bromo-2-(4-bromophenyl)-3,4-dihydro-2H-benzo[h]chromene (**7b**): pale yellow crystals, 41%, m.p. 215 °C. ^{1}H NMR (500MHz, $CDCl_3$) δ =7.84 (br.s, 1H, H_7), 7.59 (d, $J_{9,10}$ = 8.9 Hz, 1H, H_{10}), 7.46 (m, 4H, $H_{6,9}$, 2ArH), 7.26 (m, 2ArH), 7.06 (d, $J_{3,4}$ = 8.8 Hz, 1H, H_3), 4.99 (dd, 1H, J = 2.03 and 10.16 Hz), 3.05 (m, 2H, CH_2CH_2CH), 2.31, 2.10 (m+m, 1H, CH_2CH_2CH). ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 153.1, 140.7, 132.1 (2C), 131.9, 130.75, 130.65, 130.0, 128.2 (2C), 127.4, 124.2, 122.2, 120.6, 117.5, 114.2, 77.9, 29.9, 21.9. IR (KBr) cm^{-1}: 3052, 2947, 2918, 2873, 1655, 1649, 1514, 1442, 1409, 1276, 1169, 1103, 1011, 879, 800, 609, 656. Anal: Calcd. for $C_{19}H_{14}Br_2O$: C, 54.58, H, 3.37. Found: C, 54.58, H, 3.36 %.

8-Bromo-2-p-tolyl-3,4-dihydro-2H-benzo[h]chromene (**7c**): colourless crystals, 45%, m.p. 128 °C. ^{1}H NMR (500MHz, $CDCl_3$) δ =7.85 (br.s, 1H, H_7), 7.50 (m, 2H, $H_{9,10}$), 7.32 (m, 1H, H_6), 7,26, 7.12 (AA'BB' system, 4ArH), 7.04 (m, 1H, H_5), 4.99 (dd, 1H, J = 2.05 and 10.10 Hz), 3.03 (m, 2H), 2.29 (s, 3H, CH_3), 2,14 (m, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 154.0, 138.65, 138.2, 134.8, 130.45, 129.7, (2C), 128.1, 127.8, 126.9, 126.5 (2C), 124.9, 121.3, 120.15, 113.4, 77.5, 31.4, 29.8, 21.6. IR (KBr) cm^{-1}: 3025, 2953, 2927, 2848, 1659, 1620, 1452, 1392, 1216, 1142, 1092, 1022, 907, 888, 819, 784, 600, 529. UV (MeOH), λ_{max} (log ε): 242.6 (2.54). Anal. Calcd. for $C_{20}H_{17}BrO$: C, 68.00, H, 4.85. Found: C, 68.01, H, 4.85 %.

1-(2,3-Dihydro-1H-benzo[f]chromen-3-yl)-1H-imidazole (**8**): colourless crystals, 53%, m.p. 151 °C. ^{1}H NMR (500MHz, $CDCl_3$) δ =7.71 (br.s, 1H, $H_{2'}$, imidazole moiety), 7.68 (m, 2H, $H_{5,8}$), 7.57 (d, A part of AB system, $J_{9,10}$ = 8.9 Hz, 1H, H_9), 7.43 (m, 1H, H_6), 7.31 (m, 1H, H_7), 7.05 br.d, $H_{4',5'}$ imidazole moiety), 6.98 (d, B part of AB system, $J_{9,10}$ = 8.9 Hz, 1H, H_{10}), 5.82 (t, 1H, J = 5.75 Hz), 3.11 (m, 2H), 2.42 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 150.8, 136.4, 132.8, 130.2, 129.85, 129.0 (2C), 127.3, 124.5, 122.4, 118.9, 117.3, 113.3, 82.1, 24.9, 20.9. IR (KBr) cm^{-1}: 3402, 3122, 2922, 2546, 1677, 1665, 1640, 1572, 1535, 1144, 1042, 946, 863, 663, 479. UV (MeOH), λ_{max} (log ε): 226.5(2.51). Anal: Calcd. for $C_{16}H_{14}N_2O$: C, 76.78, H, 5.64, N, 11.19. Found: C, 76.76, H, 5.61, N, 11.15 %.

3-n-Butoxy-2,3-dihydro-1H-benzo[f]chromene (**9**): pale brown liquid, b.p. 197 °C/20 mmHg (36%). ^{1}H NMR (500MHz, $CDCl_3$) δ =7.73 (d, $J_{5,6}$ = 8.5 Hz, 1H, H_5), 7.65 (d, $J_{7,8}$ = 8.1 Hz, 1H, H_8), 7.53 (d, A part of AB system, $J_{9,10}$ = 8.87 Hz, 1H, H_9), 7.35 (m, 1H, H_6), 7.23 (m, 1H, H_7), 6.97 (d, B part of AB system, $J_{9,10}$ = 8.87 Hz, 1H, H_{10}), 5.19 (t, 1H, J = 2.86 Hz.), 3.74 (m, 1H), 3.49 (m, 1H), 2.95 (m, 2H), 2.09 (m, 1H), 1.98 (m. 1H), 1.42 (m, 2H), 1.18 (m, 2H), 0.75 (t, J = 6.5 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 149.9, 133.3, 129.4, 128.9, 128.7, 128.2, 123.8, 122.5, 119.6, 114.95, 97.5, 68.6, 32.2, 26.9, 19.75, 17.95, 14.3. IR (CCl_4) cm^{-1}: 3063, 2927, 2856, 1626, 1600, 1516, 1436, 1378, 1311, 1206, 1141, 1030, 956, 939, 912, 848, 773. UV (MeOH), λ_{max} (log ε): 237.8 (2.46). Anal. Calcd. for $C_{17}H_{20}O_2$: C, 79.65, H, 7.86. Found: C, 79.65, H, 7.87 %.

3-(4-Bromophenyl)-2,3-dihydro-1H-benzo[f]chromene (**10**): colourless crystals, 36 %, m.p. 145 °C. ^{1}H NMR (500MHz, $CDCl_3$) δ = 7.85 (m, 2H, $H_{5,8}$), 7.74 (d, A part of AB system, $J_{9,10}$ = 8.9 Hz, 1H, H_9), 7.37, 7.24 (m+m, 6H, $H_{6,7}$, 4H Ph moiety), 7.03 (d, B part of AB system, $S_{9,10}$ = 8.9 Hz, 1H, H_{10}), 4.92 (dd, 1H, J = 2.10 and 10.19 Hz), 2.99 (m, 2H), 2.23 (m, 1H), 2.02 (m, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 152.75, 141.0, 133.3, 132.0 (2C), 129.4, 128.9, 128.3, 128.2 (2C), 126.8, 123.8, 122.35, 122.1, 119.45, 113.9, 77.5, 30.0, 21.9. IR (KBr) cm^{-1}: 3073, 2952, 2920, 2872, 1697, 1686, 1555, 1436, 1399, 1156, 1104, 1087, 1026, 989, 904, 861, 814, 687, 553. U.V. (MeOH), λ_{max} (log ε): 239.7 (2.58). Anal: Calcd. for $C_{19}H_{15}BrO$: C, 67.27, H, 4.46. Found: C, 67.29, H, 4.47 %.

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