Phenylboronic Acid-Mediated Synthesis of 2*H*-Chromenes

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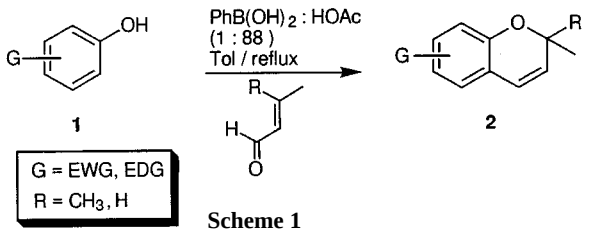
Abstract: Condensation of phenols with but-2-enal and 3-methylbut-2-enal in the presence of phenylboronic acid in acetic acid–toluene solution leads to substituted and condensed 2*H*-chromenes, constituting a mild and advantageous complement to classical routes for this class of heterocycles.

Key words: 2*H*-chromene, phenylboronic acid, condensation of phenols with unsaturated aldehydes

The central position of the 2*H*-chromene ring system in large and diverse classes of naturally occurring and biologically active heterocycles[1,2] has led to the development of a number of regimens for their preparation: a) Claisen rearrangement of propargyl phenyl ethers;[3] b) Pd-catalyzed ring closure of 2-isoprenyl phenols,[4] and c) comprehensive Lewis acid catalyzed methods.[5,6] Formulated on the basis of the important Nagata procedure for *ortho*-regiospecific electrophilic substitution of phenols,[7] general, multigram-scale boron Lewis-acid chelation-controlled preparation of *o*-substituted phenols and anilines[8] has been extensively developed and applied to the construction of tetrahydrocannabinols and their 5-aza analogs.[9] Recently, Murphy showed that condensation of citronellal with phenols in the presence of phenylboronic acid furnishes some hexahydrocannabinoids in good yields.[10,11] Herein, we report a general phenylboronic acid procedure for the preparation of substituted and condensed 2*H*-chromenes **2** by condensation of phenols **1** with unsaturated aldehydes (Scheme 1). The advantages of this method in terms of mildness of conditions and efficiency over other Lewis acid[5,6] and base[12,13,15] induced processes anticipates its broader application and is recently demonstrated in the synthesis of naturally occurring pyroxanthones from our laboratories.[14]



Scheme 1

The results are summarized in the Table. Treatment of phenols **1** with either but-2-enal (crotonaldehyde) or 3-methylbut-2-enal (senecioaldehyde) in the presence of PhB(OH)2 (1 equiv) in HOAc-toluene solution under reflux afforded the respective 2*H*-chromene derivatives **2** in modest to excellent yields. As expected on the basis of mechanistic considerations,[7,11] electron-donating groups facilitate the reaction (entries 3–6, 9–12) while electron-withdrawing substituents give less satisfactory results (entries 2, 8) and 4-nitrophenol is recovered unchanged. The reaction may be extended to the preparation of condensed 2*H*-chromenes from naphthols (entries 13–15) and from phenanthrols (entry 16). Both crotonaldehyde and senecioaldehyde undergo smooth condensation with the same phenols to give useful yields of products (compare entries 3 and 4 and entries 11 and 12).

The described procedure shows promising advantage over similar reported cyclization procedures. Thus precocene II, an insecticide (entry 9) previously synthesized in nine steps and 16% overall yield starting from ethyl 4-acetylbutyrate,[16] was obtained in one step in 91% isolated yield.[11]

In summary, the phenylboronic acid procedure for the condensation of phenols with unsaturated aldehydes constitutes a convenient, mild, and general complement to other methods[5,6,12] for the synthesis of 2*H*-chromenes.

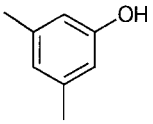
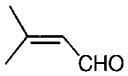
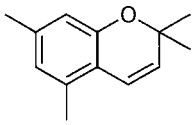
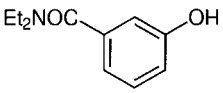
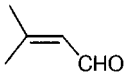
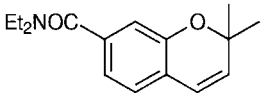
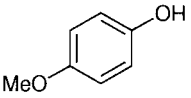
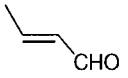
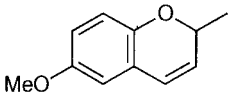
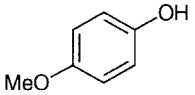
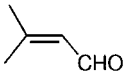
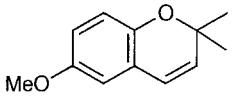
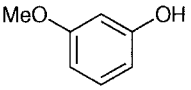
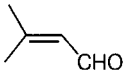
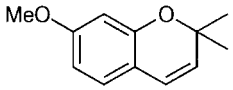
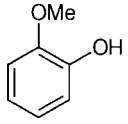
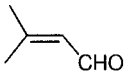
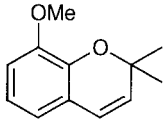
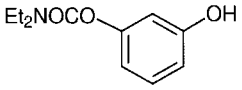
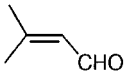
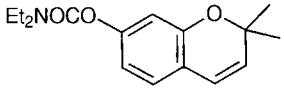
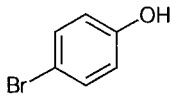
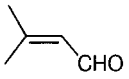
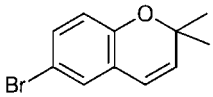
Mps were determined on a Büchi-20 apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer 983 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AM-250 and AC-200 instruments with TMS as internal standard. Mass spectra (MS) were determined on a high-resolution Varian MAT-CH7 instrument at 70 eV. Microanalyses were performed by M-H-W Laboratories, Phoenix, Ariz. With the exception of *N*,*N*-diethyl-3-hydroxybenzamide,[18] all commercial materials were purchased from Aldrich Chemical Co. or Lancaster Synthesis Ltd.

General Procedure:
A solution of phenol **1** (2.7 mmol), aldehyde (2.7 mmol), phenylboronic acid (2.7 mmol) and glacial HOAc (13.5 mL) in anhyd toluene (100 mL) was refluxed for 16 h under N_2 in an apparatus fitted with a Dean–Stark trap. Optimization of product formation was effected by TLC monitoring. The mixture was cooled, concentrated in vacuo, and the residue was extracted with several portions of CH_2Cl_2 (3 mL). The combined extract was washed successively with H_2O (15 mL), $NaHCO_3$ (20 mL), and brine (15 mL), dried (Na_2SO_4), the solvent was evaporated in vacuo, and the crude product was purified by flash chromatography on silica gel (EtOAc–hexane 1:9 eluent).

2,2,5, 7-Tetramethyl-2H-1-benzopyran (entry 1): bp 98–102 °C/0.2 Torr.
^{1}H NMR ($CDCl_3$) δ = 1.40 (s, 6H), 2.22 (s, 3H), 2.24 (s, 3H), 5.57 (d, J = 10 Hz, 1H), 6.45–6.50 (m, 3H).
^{13}C NMR ($CDCl_3$) δ = 152.9, 138.5, 133.5, 129.3, 123.2, 119.2, 117.1, 114.8, 27.7 (two), 21.3, 18.2.
IR (neat) ν = 2974, 2922, 1613, 1564, 1311, 1212 cm$^{-1.}$
MS (rel intensity) *m/e* 188(10), 173(100), 128(7), 155(7), 91(5), 79(5).
Anal. Calcd. for $C_{13}H_{16}O$: C, 82.93; H, 8.56; Found: C, 82.74; H, 8.70.

2,2-Dimethyl-7-(N,N-diethylcarboxamido)-2H-1-benzopyran (entry 2): oil, bp 136–140°C/0.2 Torr.
IR (neat) ν = 2950, 1728, 1623, 1556, 1503, 1446, 1215 cm$^{-1.}$
^{1}H NMR ($CDCl_3$) δ = 1.06–1.26 (br m, 6H), 1.42 (s, 6H), 3.28–3.50 (br), 5.64 (d, J = 10 Hz, 1H), 6.31 (d, J – 10 **H**z, 1H), 6.76 (s, 1H), 6.82 (dd, J = 1.5, 7.5 Hz, 1H), 6.97 (d, J = 7.5 Hz, 1H).

Table. Synthesis of Substituted 2H-Chromenes (**2**)

Entry	ArOH	RCHO	Product	Yield (%)
1				65
2				25
3				70
4				70
5				83
6				50
7				67
8				35

^{13}C NMR($CDCl_3$) δ = 153.5, 153.3, 151.8, 129.3, 126.0, 121.3, 117.9, 113.4, 109.6, 75.9, 41.7, 27.7, 13.8, 13.0.
MS (rel intensity) *m/e* 259(50), 244(100), 187(95), 144(90), 115(60); HRMS Calcd. for $C_{16}H_{21}NO_2$: 259.15721; Found: 259.15678.

6-Methoxy-2-methyl-2H-1-benzopyran (entry 3):
bp 70–74°C/0.22 Torr (lit.[17] bp 86 °C/0.9 Torr).
^{1}H NMR ($CDCl_3$) δ= 1.41 (d, *J* = 6 Hz, 3H), 3.74 (m, 3H), 4.89–4.94 (m, 1H), 5.68 (dd, *J* = 9.7, 3.0 Hz, 2H), 6.34 (d, *J* = 9.7 Hz, 1H), 6.54 (d, *J* = 3.0 Hz, 1H), 6.63–6.73 (m, 2H).
HRMS Calcd. for $C_{11}H_{12}O_2$: 176.08372; Found: 176.08368.

6-Methoxy-2,2-dimethyl-2H-1-benzopyran (entry 4):
bp 62–65°C/0.22 Torr (lit.[19] bp 132–136°C/15 Torr).
^{1}H NMR ($CDCl_3$) δ = 1.40 (s, 6H), 5.53 (d, *J* = 10 Hz, 1H), 6.28 (d, *J* = 10 Hz, 1H), 6.54 (d, *J* = 2.3 Hz, 1H), 6.67–6.69 (m, 2H).

7-Methoxy-2,2-dimethyl-2H-1-benzopyran[11] (entry 5): colorless oil.
^{1}H NMR ($CDCl_3$) δ = 1.42 (s, 6H), 3.78 (s, 3H), 5.46 (d, *J* = 16 Hz, 1H), 6.27 (d, *J* = 16 Hz, 1H), 6.37–6.43 (m, 2H), 6.88 (d, *J* = 6 Hz, 1H).
^{13}C NMR($CDCl_3$) δ = 160.6, 154.1, 127.5, 126.7, 121.7, 114.4, 106.3, 101.9, 76.0, 54.9, 27.8. HRMS Calcd. for $C_{12}H_{14}O_2$: 190.09937, Found: 190.09860.

8-Methoxy-2,2-dimethyl-2H-1-benzopyran (entry 6): bp 80–84°C/0.2 Torr (lit.[13] bp 115 °C/2 Torr).
^{1}H NMR ($CDCl_3$) δ = 1.48 (s, 6H), 3.85 (s, 3H), 5.61 (d, *J* = 10 Hz, 1H), 6.30 (d, *J* = 10 Hz, 1H), 6.59–6.68 (m, 1H), 6.77–6.78 (m, 2H).

2,2-Dimethyl-7-(N,N-diethyl O-carbamoyl)-2H-1-benzopyran (entry 7): oil.
^{1}H NMR ($CDCl_3$) δ = 1.15–1.29 (br m, 3H), 1.41 (s, 6H), 3.33–3.44 (br m, 4H), 5.54 (d, *J* = 9.8 Hz, 1H), 6.29 (d, *J* = 9.8 Hz, 1H), 6.56 (d, *J* = 2.5 Hz, 1H), 6.61 (dd, *J* = 2.3, 8.0 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H).
^{13}C NMR ($CDCl_3$) δ = 13.0, 13.8, 27.7, 41.7, 75.9, 109.6, 113.4, 117,9, 121.3, 126.0, 129.3, 151.8, 153.3, 153.5.
HRMS Calcd. for $C_{16}H_{21}NO_3$: 275.15213; Found: 275.15201.

Table. (continued)

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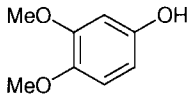
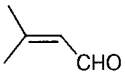
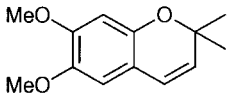
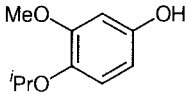
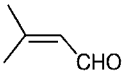
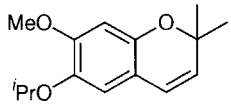
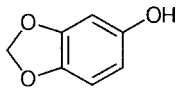
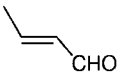
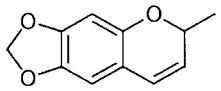
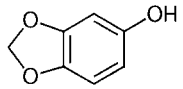
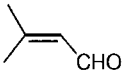
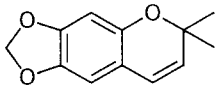
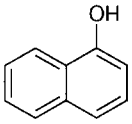
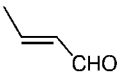
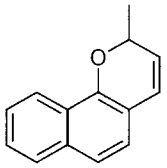
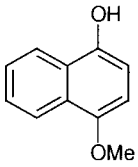
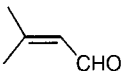
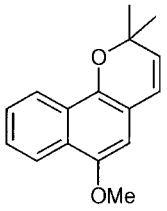
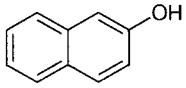
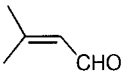
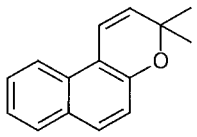
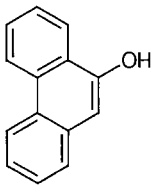
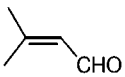
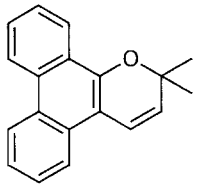
9				91
10				70
11				60
12				85
13				60
14				95
15				95
16				48

6-Bromo-2,2-dimethyl-2H-1-benzopyran (entry 8): oil, bp 93–96 °C/0.2 Torr (lit.[21] bp 116 °C/5 Torr).
^{1}H NMR($CDCl_3$) δ = 1.41 (s, 6H), 5.63 (d, J = 10 Hz, 1H), 6.24 (d, J = 10 Hz, 1H), 6.64 (d, J = 8.5 Hz, 1H), 7.07 (br s, 1H).

6,7-Dimethoxy-2,2-dimethyl-2H-1-benzopyran (entry 9): mp 43–45°C, Et_2O/Hexanes (lit.[16] mp 46–47 °C).
^{1}H NMR ($CDCl_3$) δ = 1.41 (s, 6h), 3.82 (s, 3H), 3.84 (s, 3H), 5.48 (d, J = 9.7 Hz, 1H), 6.24 (d, J = 9.7 Hz, 1H), 6.42 (s, 1H), 6.53 (s, 1H).
^{13}C NMR ($CDCl_3$) δ = 149.3, 146.9, 142.7, 127.7, 121.6, 112.6, 109.5, 100.6, 75.4, 56.0, 55.4, 27.2; HRMS Calcd. for $C_{13}H_{16}O_3$: 220.10913; Found: 220.10904.

2,2-Dimethyl-6-isopropoxy-7-methoxy-2H-1-benzopyran (entry 10): bp 130–135 °C/0.5 Torr.
IR (neat) ν = 2974, 1614, 1572, 1503, 1362, 1124 cm^{-1}.
^{1}H NMR ($CDCl_3$) δ = 1.31 (d, J = 6 Hz, 6H), 1.41 (s, 6H), 3.79 (s, 3H), 4.33 (m, 1H), 5.46 (d, J = 10 Hz, 1H), 6.21 (d, J = 10 Hz, 1H), 6.39 (s, 1H), 6.57 (s, 1H).
MS (rel intensity) *m/e* 248(20), 233(25), 191(100), 176(10), 91(10).
Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.11; Found: C, 72.46; H, 7.96.

6,7-Dioxymethylene-2-methyl-2H-1-benzopyran (entry 11): mp 70–72°C, Et_2O/Hexanes.
IR (film) ν = 2983, 2901, 2842, 1642, 1615, 1603, 1256, 1208 cm^{-1}.

^{1}H NMR (CDCl3) δ = 1.40 (d, J = 6.6 Hz, 3H), 4.86–4.89 (m, 1H), 5.52 (dd, J = 3, 10 Hz, 1H), 5.87 (s, 2H), 6.26 (d, J = 10 Hz, 1H), 6.38 (s, 1H), 6.46 (s, 1H).
MS (rel intensity) *m/e* 190(20), 175(100), 117(5), 77(10).
Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.46; H, 5.29; Found: C, 69.46; H, 5.32.

2,2-Dimethyl-6,7-dioxymethylene-2H-1-benzopyran[4] (entry 12): bp 113–116°C/0.2 Torr.
^{1}H NMR (CDCl3) δ = 1.39 (s, 6H), 5.46 (d, J = 10 Hz, 1H), 5.87 (s, 2H), 6.19 (d, J = 10 Hz, 1H), 6.37 (s, 1H), 6.46 (s, 1H).
^{13}C NMR ($CDCl_3$) δ = 148.1, 147.5, 128.0, 122.2, 114.1, 105.5, 100.8, 98.9, 27.4 (two).
IR (neat) ν = 2975, 2894, 1613, 1476, 1370, 1259, 1200 cm^{-1}.
MS (rel intensity) *m/e* 204(15), 189(100), 159(5), 131(10), 77(10).
Anal. Calcd. for $C_{12}H_{12}O$: C, 70.57; H, 5.92; Found: C, 70.68, H, 6.03.

2-Methyl-2H-naphtho[1,2-b]pyran (entry 13): colorless oil.
^{1}H NMR ($CDCl_3$) δ = 1.53 (d, J = 6.6 Hz, 3H), 5.16–5.70 (m, 1H), 5.69 (dd, J = 3.3, 9.7 Hz, 1H), 6.49 (dd, J = 1.6, 9.7 Hz, 1H), 7.13 (d, J = 8.3 Hz, 1H), 7.34 (d, J = 8.2 Hz, 1H), 7.39–7.44 (m, 2H), 7.70–7.74 (m, 1H), 8.14–8.18 (m, 1H).
^{13}C NMR ($CDCl_3$) δ = 148.7, 134.4, 127.5, 126.1, 125.2, 124.7, 124.5, 124.1, 121.8, 120.1, 116.0, 71.9, 21.1.
HRMS Calcd. for $C_{14}H_{12}O$: 196.08880; Found: 196.08911.

6-Methoxy-2,2-dimethyl-2H-naphtho[1,2-b]pyran (entry 14): mp 61–64°C, Et_2O/Hexanes (lit.[20] 62°C).
^{1}H NMR δ = 1.48 (s, 6H), 3.94 (s, 3H), 5.64 (d, J = 10 Hz, 1H), 6.30 (d, J = 10 Hz, 1H), 6.50 (s, 1H), 7.38–7.49 (m, 2H), 8.12–8.15 (m, 2H).

2,2-Dimethyl-2H-naphtho[2,1-b]pyran[15] (entry 15): oil.
^{1}H NMR ($CDCl_3$) δ = 1.48 (s, 3H), 1.49 (s, 3H), 5.71 (d, J = 9.6 Hz, 1H), 7.02 (d, J = 9.6 Hz, 1H), 7.31–7.35 (m, 1H), 7.43–7.49 (m, 1H), 7.64 (d, J = 8.8 Hz, 1H), 7.74 (d, J = 8.1 Hz, 1H), 7.94 (d, J = 8.6 Hz, 1H).
^{13}C NMR ($CDCl_3$) δ = 150.9, 129.8, 129.2, 129.1, 128.4, 126.3, 123.2, 121.1, 118.3, 118.1, 113.5, 75.8, 27.5.
HRMS Calcd. for $C_{15}H_{14}O$: 210.10445; Found: 210.10367.

2,2-Dimethyl-2H-phenanthro[9,10-b]pyran (entry 16): oil.
^{1}H NMR ($CDCl_3$) δ = 1.59 (s, 6H), 5.81 (d, J = 9.9 Hz, 1H), 7.10 (d, J = 9.9 Hz, 1H), 7.42–7.65 (m, 4H), 8.02–8.07 (m, 1H), 8.37–8.44 (m, 1H), 8.61–8.69 (m, 2H).
^{13}C NMR ($CDCl_3$) δ = 146.7, 131.0, 129.3, 128.8, 126.9, 126.4, 126.3, 125.9, 124.0, 123.0, 122.6, 122.4, 121.8, 118.7, 110.3, 76.2, 27.4.
HRMS Calcd. for $C_{19}H_{16}O$: 260.12010; Found: 260.11955.

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