Synthesis of 6-Cyano-2,2-dimethyl-2*H*-1-benzopyran and Other Substituted 2,2-Dimethyl-2*H*-1-benzopyrans†

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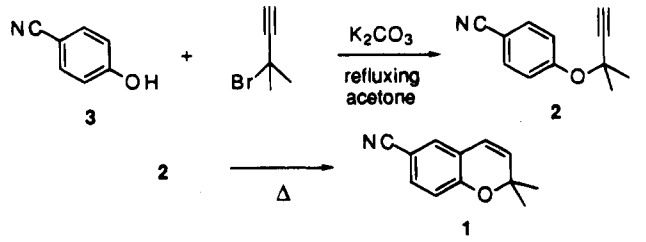
A practical synthesis of 6-cyano-2,2-dimethyl-2*H*-1-benzopyran (**1**) has been developed. This process involves the pyridine-catalyzed condensation of 1,1-diethoxy-3-methyl-2-butene (**6**) with 4-cyanophenol (**3**) in toluene or xylene at elevated temperatures. The development of this process, including an evaluation of solvents, bases, acid catalysts, and alternative acetals, along with an improved synthesis of 1,1-diethoxy-3-methyl-2-butene, is discussed. Using this method, a variety of other substituted 2,2-dimethyl-2*H*-1-benzopyrans were synthesized.

Introduction

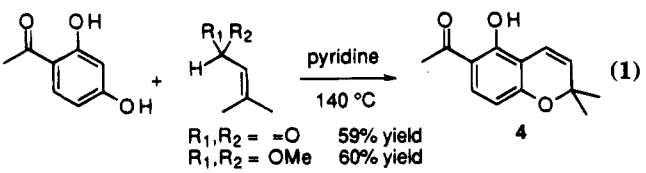
In recent years there has been increased interest in the synthesis of 2*H*-1-benzopyrans (chromenes) due to the number of compounds which possess this subgroup and show antidepressant, antihypertensive, and hypoglycemic activity as well as other biological effects.[1,2] The literature contains a variety of synthetic approaches to the chromene ring structure, much of which has been compiled into comprehensive reviews.[3] As part of an ongoing project, we also were interested in a practical synthesis of chromene **1**. With the exception of the Harfenist–Thom rearrangement/cyclization of propargyl ether **2** to **1** (Scheme 1),[2a,4] the literature procedures appeared unsatisfactory.[5] While investigating the feasibility of this approach,[6] we also searched for an alternative route to **1** which is the subject of this paper.

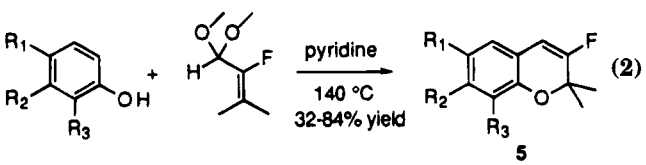
In 1969, Crombie and co-workers demonstrated that addition of excess 3-methyl-2-butenal or the corresponding dimethyl acetal to 2,4-dihydroxyacetophenone (~1 equiv of pyridine, 140 °C) afforded chromene **4** in ~60% yield (eq 1).[7,8] In a similar vein, Camps and co-workers[9] reported that heating a mixture of a phenol, acetal, and

Scheme 1



pyridine at 140 °C[10] provided fluorinated chromenes **5** in 32–84% yields (eq 2). The reaction rate was rapid





when the phenol was substituted with electron-donating groups whereas electron-withdrawing groups retarded the reaction and required the use of a large excess of acetal. Consequently, implementation of this methodology for the preparation of **1** from 4-cyanophenol appeared to be questionable. Regardless, an investigation into this approach was undertaken and after considerable experimentation a practical synthesis of **1** and other chromenes bearing electron-withdrawing substituents was developed.

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(1) Cruz-Almanza, R.; Pérez-Flores, F.; Lemini, C. *Heterocycles* **1994**, *37*, 759 and references cited therein.

(2) (a) Evans, J. M.; Fake, C. S.; Hamilton, T. C.; Poyser, R. H.; Watts, E. A. *J. Med. Chem.* **1983**, *26*, 1582. (b) Ashwood, V. A.; Buckingham, R. E.; Cassidy, F.; Evans, J. M.; Faruk, E. A.; Hamilton, T. C.; Nash, D. J.; Stemp, G.; Willcocks, K. *J. Med. Chem.* **1986**, *29*, 2194. (c) Bergmann, R.; Gericke, R. *J. Med. Chem.* **1990**, *33*, 492. (d) Gericke, R.; Harting, J.; Lues, I.; Schittenhelm, C. *J. Med. Chem.* **1991**, *34*, 3074. (e) Cassidy, F.; Evans, J. M.; Hadley, M. S.; Haladij, A. H.; Leach, P. E.; Stemp, G. *J. Med. Chem.* **1992**, *35*, 1623. (f) Atwal, K. S.; Grover, G. J.; Ahmed, S. Z.; Ferrara, F. N.; Harper, T. W.; Kim, K. S.; Sleph, P. G.; Dzwonczyk, S.; Russell, A. D.; Moreland, S.; McCullough, J. R.; Normandin, D. E. *J. Med. Chem.* **1993**, *36*, 3971.

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(4) Harfenist, M.; Thom, E. *J. Org. Chem.* **1972**, *37*, 841 and references cited therein.

(5) (a) Buckle, D. R.; Connor, S. C.; Eggleston, D. S.; Faller, A.; Pinto, I. L.; Readshaw, S. A.; Smith, D. G. *J. Chem. Soc., Perkin Trans 1* **1992**, 769. (b) Bergmann, R.; Gericke, R. *J. Med. Chem.* **1990**, *33*, 492.

(6) Also see the modification of the procedure in Scheme 1 by Godfrey, J. D., Jr.; Mueller, R. H.; Sedergran, T. C.; Soundararajan, N.; Colandrea, V. A. *Tetrahedron Lett.* **1994**, *35*, 6405.

(7) Bandaranayake, W. M.; Crombie, L.; Whiting, D. A. *J. Chem. Soc., Chem. Commun.* **1969**, 970.

(8) For additional work in this area see: (a) Crombie, L.; Ponsford, R. *Tetrahedron Lett.* **1968**, *43*, 4557. (b) Crombie, L.; Ponsford, R. *J. Chem. Soc. C* **1971**, 788. (c) Crombie, L.; Ponsford, R. *J. Chem. Soc. C* **1971**, 796. (d) Bandaranayake, W. M.; Crombie, L.; Whiting, D. A. *J. Chem. Soc. C* **1971**, 804. (e) Bandaranayake, W. M.; Crombie, L.; Whiting, D. A. *J. Chem. Soc. C* **1971**, 811. (f) Clarke, D. G.; Crombie, L.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1007. (g) Asgill, J. O.; Crombie, L.; Whiting, D. A. *J. Chem. Soc., Chem. Commun.* **1978**, 59. (h) Lamcharfi, E.; Menguy, L.; Zamarlik, H. *Synth. Commun.* **1993**, *23*, 3019.

(9) Camps, F.; Coll, J.; Messeguer, A.; Pericás, M. A. *J. Heterocycl. Chem.* **1980**, *17*, 1377.

(10) Generally in a 1:2:1 ratio of phenol:acetal:pyridine.

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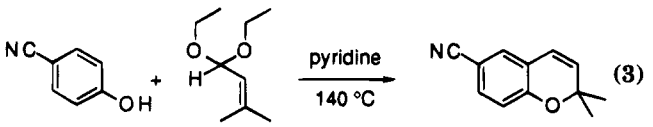
Results and Discussion

In order to initiate our investigation into the synthesis of **1**, an efficient preparation of an acetal of 3-methyl-2-butenal was required.[11] While the synthesis of 3-methyl-2-butenal dialkyl acetals has been reported, the dimethyl and diethyl acetals were isolated only in low yields after tedious distillations.[8e,12] Synthesis of the diethyl acetal from ethanol, triethyl orthoformate, and catalytic *p*-toluenesulfonic acid was unsuccessful due to polymerization of the aldehyde under the reaction conditions. Therefore, we investigated the use of other mild acids to catalyze this reaction and ultimately found that the use of $KHSO_4$ produced **6** in 86% yield after a simple distillation from K_2CO_3.[13-15]

Following the Camps and Crombie procedures, **3** was reacted with **6** in 1.2 molar equiv of pyridine at 156 °C (eq 3). While the reaction produced a trace of **1**, the



(3)

3 **6** **1**

majority of the material in the crude product appeared to be polymerized **6** by ^1H NMR and mass spectrometry. In an effort to minimize polymerization, we investigated the use of an inert solvent and milder conditions. Initially, the reactions were conducted in refluxing toluene (2 M), producing **1** in moderate yield and purity (Table 1, entries 1–3).[16] Next, the concentration of **3** was decreased to 0.4 M and the stoichiometry of base and acetal was further optimized (Table 1, entries 4–13).

A trend toward higher yields and GC purities was observed with decreasing pyridine stoichiometry. The optimum conditions proved to be 0.25 molar equiv of pyridine with portionwise addition of 2 equiv of **6**, producing **1** in 82% yield with excellent purity (Table 1, entry 7).[17] The beneficial effect of using catalytic pyridine might be attributed to the phenol acting in a dual capacity as reactant and acid-catalyst for activation of the acetal to nucleophilic attack (see below). Higher levels of pyridine presumably buffer the acid necessary to activate the acetal. This hypothesis prompted us to examine a range of acid and base additives (Tables 2 and 3). Of the bases studied, pyridine and 3-picoline provided optimum results. None of the acid additives studied increased the yield of **1**. Apparently there is a narrow pK_a window for effective catalysis of this reaction.

Table 1. Initial Optimization Studies for the Synthesis of 1

entry	mg of **3**	equiv of pyridine	equiv of **6**	% yield[a]	% GC area
1	500	2.06	1.02[b]	57	83
2	500	1.04	1.64[b]	78	81
3	500	2.06	2.08[b]	66	83
4	250	2.06	2.32[c]	67	92
5	200	1.02	2.15[c]	74	97
6	200	0.52	2.05[c]	72	98
7	200	0.26	2.13[c]	82	96
8	200	1.99	1.07[b]	33	98
9	201	0.99	1.07[b]	38	98
10	205	0.51	1.01[b]	51	98
11	200	0.25	1.08[b]	60	94
12	200	0.11	1.09[b]	58	83
13	201	0.00	1.08[b]	–	0

[a] Yields of isolated products corrected for residual solvent present by ^1H NMR. [b] Total reaction time was 24 h. [c] The first molar equivalent of **6** was added at the start of the reaction with an additional equivalent of **6** added after 24 h. Total reaction time was 48 h.

Table 2.[a] Effect of Various Base Catalysts on the Yield of 1

entry	base	pK_a[18]	results[b]
1	DBU	14.3	34% yield
2	Bu_3N	9.93	41% yield
3	*N*-methylmorpholine	6.62	62% yield
4	4-DMAP	6.09	54% yield
5	3-picoline	5.63	81% yield
6	pyridine	5.25	79% yield
7	quinoline	4.81	31% yield
8	DABCO	2.95, 8.60	62% yield

[a] The reactions were performed using 0.25 equiv of base and 1 equiv of **6** with an additional 0.8 equiv of **6** added after 7 h. The reactions were run in *p*-xylene at 120 °C; total reaction time was 24 h. [b] Yields of isolated products corrected for residual solvent (^1H NMR).

Table 3. Effect of Various Acid Catalysts on the Yield of 1

entry	acid	equiv of acid	equiv of 3-picoline	results/% GC area
1[a]	PPTS	0.25	0.50	no **1** detected
2[a]	Bu_4NHSO_4	0.25	0.49	no **1** detected
3[a]	$(NH_4)_2SO_4$	0.25	0.49	no **1** detected
4[b]	benzoic acid	0.26	0.50	51% yield[c]/92%
5[b]	fumaric acid	0.25	0.50	55% yield[c]/66%
6[b]	fumaric acid	0.13	0.52	79% yield[c]/83%

[a] The reactions were performed using 1 equiv of **6** and the indicated acid in *p*-xylene at 120 °C. Total reaction time was 6 h. [b] The reactions were performed using 1 equiv of **6** and the indicated acid in *p*-xylene at 119 °C. Total reaction time was 24 h. [c] Yield of isolated product corrected for residual solvent (^1H NMR).

The mechanism in Scheme 2[8f] illustrates the complexity of the balancing effects of acid- and base-catalysis. Base-catalyzed alkylation of **3** by the activated acetal (oxonium ion) gives dienone **7**. Tautomerization to **8**, followed by elimination of ethanol, forms **9**. Finally, electrocyclic ring closure provides **1**.

In the previous examples, 2 equiv of acetal **6** was required for complete conversion of **3** to **1**, presumably due to competitive polymerization of **6**. Since cyclic acetals are more stable to acid than dialkyl acetals,[19] **10**–**12** were synthesized[20] as alternatives (Figure 1). However, we recognized that added stability would be offset

(11) Numerous attempts to condense 4-cyanophenol with 3-methyl-2-butenal under acidic or basic conditions failed due to the aldehyde's propensity to polymerize under the reaction conditions.

(12) (a) Hoepfner, W.; Weyerstahl, P. *Liebigs Ann. Chem.* **1986**, 99. (b)VanAllan, J. A. In *Organic Syntheses*; John Wiley & Sons: New York, 1963; Coll. Vol. IV, p 21.

(13) Other mild acids investigated include triethylamine hydrochloride, pyridinium 4-toluenesulfonate, tetrabutylammonium hydrogen sulfate, and ammonium bisulfate; however, all proved to be inferior to potassium hydrogen sulfate.

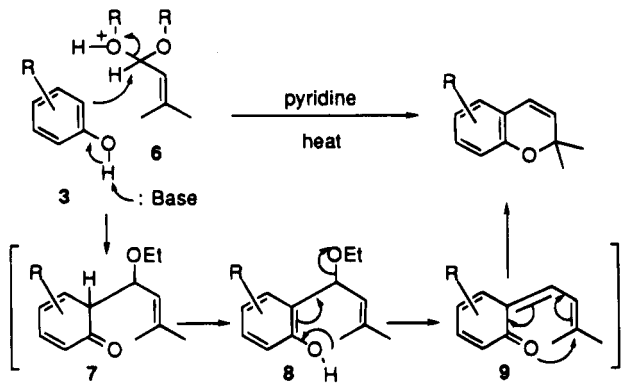
(14) Acetal **6** was also synthesized from 3-methyl-2-butenal by treatment with ethoxytrimethylsilane and TMSOTf in CH_2Cl_2 in 79% yield. See the procedures of (a) Yoshimura, J.; Horito, S.; Hashimoto, H. *Chem. Lett.* **1981**, 375. (b) Hwu, J. R.; Leu, L.-C.; Robl, J. A.; Anderson, D. A.; Wetzel, J. M. *J. Org. Chem.* **1987**, *52*, 188.

(15) For an alternative synthesis of **6** from (2-methylpropenyl)-magnesium bromide and triethyl orthoformate, see Canepa, C.; Prandi, C.; Sacchi, L.; Venturello, P. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1875.

(16) We found that the reaction did not proceed at <100 °C; hence our choice of solvent was limited. The reaction performed equally well in both toluene and xylenes (110–120 °C), but the crude products were heavily contaminated with unknown impurities when the reaction was run in DMF or dodecane. Conversely, Crombie and co-workers observed "no significant reduction in yield" when their reactions were conducted in DMSO, decalin, or HMPA.

(17) Crombie and co-workers observed a decrease in yield when using 0.1 molar equiv of pyridine.[8f]

Scheme 2



by decreased reactivity and this was proven experimentally. Under the optimized conditions, dioxolane **10** produced **1** in 30% yield while dioxanes **11** and **12** afforded negligible amounts (<3%) of **1**.

As discussed above, in small scale reactions (≤500 mg of **3**), the condensation of **3** with **6** was efficiently achieved. However, when the input of **3** was increased even moderately to 1.50 g, the yield fell to 59%. We also observed that the internal temperature fell to 100 °C as the reaction progressed. The apparent explanation was that the constant headspace volume in the reaction vessel was unable to hold increasing concentrations of vaporized ethanol, resulting in condensation and thus lowering the internal temperature. This is consistent with a separate experiment in which we observed an exceptionally slow reaction rate at internal temperatures of ≤100 °C. The problem of lowered reaction temperature was solved by continuous removal of the ethanol by distillation. In order to avoid codistillation of the reaction solvent and base, *p*-xylene and 3-picoline were employed in place of toluene and pyridine.[21,22] Removal of ethanol in this fashion produced a faster reaction and allowed for a substantially decreased charge of **6**. A 15 g input of **3** required only 1.33 equiv of **6** and produced **1** in 89% crude yield (GC purity 97%) and 66% crystallized yield while 70 g of **3** and 1.24 equiv of **6** produced **1** in 62% crystallized yield.[23]

This methodology was also used for the synthesis of other substituted chromenes (Scheme 3) with the results summarized in Table 4. Of the phenols studied, those substituted in the para-position with electron-withdrawing groups produced the desired chromenes in much higher yields than those substituted with electron-donating groups, in contrast to previous literature results.[9] These latter results are consistent with the need for the phenol to function as an acid catalyst as discussed above. In this vein, 4-methylphenol, 4-methoxyphenol,

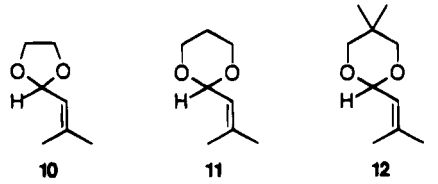
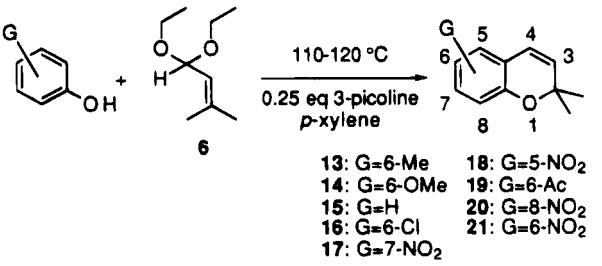


Figure 1.

Scheme 3



and phenol produced the corresponding chromene derivatives (identified by NMR and mass spectral analyses) in low yields and purities. Employment of 3-nitrophenol resulted in a 6:1 mixture of chromenes **17** and **18** which were partially separable by chromatography, while the use of 2-nitrophenol generated a very low yield of the desired chromene due to poor conversion.

Conclusion

We have developed a synthesis of 2,2-dimethylchromenes from electron-deficient phenols which is complementary to that of Crombie and Camps. This methodology involves an acid- and base-catalyzed condensation of a phenol with 3-methyl-2-butenal diethyl acetal in toluene or xylene. On larger scales, we found that the continuous removal of ethanol by distillation resulted in a faster reaction and allowed for a lower charge of acetal.

Experimental Section

General. All solvents and reagents were purchased from either Aldrich Chemical Co. (Milwaukee, WI) or Lancaster Synthesis Inc. (Windham, NH) and were used without further purification. Gas chromatography analyses (GC) were carried out on a Varian 3400 gas chromatograph with a 1/8 in. × 2 m 5% Carbowax column. Melting points are uncorrected. NMR chemical shifts are expressed in parts per million (δ) downfield from internal tetramethylsilane. All infrared, mass spectrometry, and elemental analyses were performed by the Analytical Research and Development Department, Bristol-Myers Squibb Pharmaceutical Research Institute. Flash chromatography was performed with E. Merck 240–400 mesh silica gel.

6-Cyano-2,2-dimethylchromene (1). A reaction flask equipped with a distilling head was sequentially charged with **6** (26.59 g, 168.00 mmol), *p*-xylene (300 mL), **3** (15.00 g, 125.92 mmol), and 3-picoline (3.0 mL, 30.83 mmol). The reaction mixture was heated to an internal temperature of 115 °C. After 24 h the reaction mixture was cooled to room temperature. The clear, golden reaction mixture was diluted with EtOAc (150 mL) and washed with 1 N HCl (1 × 400 mL, 1 × 200 mL). The acidic, aqueous washes were back-extracted with EtOAc (100 mL). The combined organic phases were washed with 1 N NaOH (1 × 400 mL, 1 × 200 mL). The basic, aqueous washes were back-extracted with EtOAc (100 mL). The combined organic phases were washed with saturated aqueous NaCl (300 mL), dried ($MgSO_4$), filtered, and concentrated to a golden liquid (20.85 g). A portion of the crude product (20.22 g) was crystallized from hexanes (20.0 mL). The crystals were isolated by filtration, washed with 0 °C hexanes (1 × 6 mL, 2

(18) The pK_a values were obtained from either: (a) *Handbook of Tables for Organic Compound Identification*; CRC: Cleveland, 1976; pp 436–439; (b) Leffek, K. T.; Pruszynski, P.; Thanapaalasingham, K. *Can. J. Chem.* **1989**, *67*, 590; or (c) Aldrich Chemical Co., Technical Service, Milwaukee, WI.

(19) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; 2nd ed.; John Wiley & Sons: New York, 1991; Chapter 4.

(20) (a) Yoshimura, J.; Horito, S.; Hashimoto, H. *Chem. Lett.* **1981**, 375. (b) Hwu, J. R.; Leu, L.-C.; Robl, J. A.; Anderson, D. A.; Wetzel, J. M. *J. Org. Chem.* **1987**, *52*, 188. (c) BASF AG, GB Patent 1 465 512, 1977.

(21) Toluene (bp 111 °C), *p*-xylene (bp 138 °C), pyridine (bp 115 °C, pK_a 5.25), and 3-picoline (bp 144 °C, pK_a 5.63).

(22) The distillate was typically >98% ethanol with the remainder *p*-xylene.

(23) While **1** is very soluble in all common organic solvents, it was isolated fairly efficiently by crystallization from hot hexanes. The resulting mother liquor was largely **1**.

Table 4 Synthesis of Substituted 2,2-Dimethyl-2*H*-1-benzopyrans

phenol	phenol pK_a[18a]	equiv of **6**[a]	product	results
4-methylphenol	10.26	1.04 + 0.79	**13**	14% yield[b]
4-methoxyphenol	10.20	1.13 + 0.69	**14**	19% yield[b]
phenol	9.99	1.10 + 0.67	**15**	14% yield[b]
4-chlorophenol	9.38	1.01 + 0.80	**16**	62% chromatographed yield
3-nitrophenol	8.38	1.20 + 0.60	**17**	22% chromatographed yield
4-acetylphenol	8.05	1.22 + 0.68	**19**	64% chromatographed yield
4-cyanophenol	7.95	1.33	**1**	66% crystallized yield
2-nitrophenol	7.21	1.20 + 0.60	**20**	2% chromatographed yield
4-nitrophenol	7.16	1.90	**21**	65% chromatographed yield

[a] First addition followed by second addition. [b] Estimated yield of isolated product after correction for residual solvent (^{1}H NMR) and purity (GC analysis).

× 7 mL), and dried to afford 14.91 g (66% yield) of **1** as off-white crystals, mp 47 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.37 (dd, J = 8.2 and 2.1 Hz, 1H), 7.24 (d, J = 2.1 Hz, 1H), 6.79 (d, J = 8.2 Hz, 1H), 6.29 (d, J = 10.0 Hz, 1H), 5.71 (d, J = 10.0 Hz, 1H), 1.46+ (s, 3H), 1.46− (s, 3H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 156.6, 133.2, 132.1, 130.0, 121.6, 120.5, 119.1, 117.1, 103.6, 77.7, 28.2, 28.2. IR (KBr pellet): 3065, 2994, 2972, 2936, 2224, 1638, 1603, 1485, 1464, 1368, 1279, 1269, 1215, 1167, 1148, 1134, 1105, 961, 953, 937, 901, 843, 829, 789, 768, 716 cm^{-1}. Anal. Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.54; H, 6.00; N, 7.66.

1,1-Diethoxy-3-methyl-2-butene (6). To absolute EtOH (52 mL, 892 mmol) at 4 °C (internal temperature) were added triethyl orthoformate (29.7 mL, 178 mmol) and 3-methyl-2-butenal (17.2 mL, 178 mmol). The clear, colorless solution was further cooled to 2 °C (internal temperature), and then potassium hydrogen sulfate (1.28 g, 9.38 mmol) was added. After a 10 °C exotherm, the reaction mixture was allowed to warm to 21 °C over 45 min and then allowed to stir for an additional 15 min. Insoluble material was removed by filtration and rinsed with absolute EtOH (5 mL). To the combined filtrate and washing was added anhydrous K_2CO_3 (2.62 g, 18.92 mmol). After stirring for 1 h the solid material was removed by filtration and rinsed with absolute EtOH (5 mL). The acetal **6** was isolated as a clear, colorless liquid by vacuum distillation (24.14 g, 86% yield, 117.0−118.5 °C at 171−172 mm Hg). ^{1}H NMR (270 MHz, C_6D_6): δ 5.23 (br d, J = 6.5 Hz, 1H), 4.96 (d, J = 6.5 Hz, 1H), 3.4−3.1 (m, 4H), 1.33 (s, 3H), 1.30 (s, 3H), 0.88+ (t, J = 7.0 Hz, 3H), 0.88− (t, J = 7.0 Hz, 3H). ^{13}C NMR (67.8 MHz, C_6D_6): δ 136.5, 124.5, 98.9, 60.0, 60.0, 25.5, 18.4, 15.6, 15.6. IR (neat, thin layer): 2976, 2932, 2915, 2880, 1680, 1447, 1377, 1358, 1348, 1206, 1146, 1115, 1086, 1053, 1017, 991 cm^{-1}.

General Procedure for Chromenes 13−21. A reaction flask equipped with a distilling head was sequentially charged with **6** (see Table 4), *p*-xylene (20 mL/g starting phenol), requisite phenol (1−3 g), and 3-picoline (0.25 equiv). The reaction mixture was heated to an internal temperature of ~118 °C. Where applicable, the second charge of **6** was added after ~6 h (Table 4), and then heating was continued for a total reaction time of 24 h. After cooling to room temperature the reaction mixture was diluted with EtOAc, washed with 1 N HCl, 1 N NaOH, and saturated aqueous NaCl (300 mL), dried ($MgSO_4$), and concentrated to an oil.

6-Chloro-2,2-dimethylchromene (16). A 3.00 g input of 4-chlorophenol produced 2.81 g of **16** (62% yield) as a clear, colorless oil after purification by column chromatography (silica gel; hexanes:EtOAc, 98:2). ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.03 (dd, J = 8.2 and 2.9 Hz, 1H), 6.93 (d, J = 2.9 Hz, 1H), 6.69 (d, J = 8.2 Hz, 1H), 6.23 (d, J = 10.1 Hz, 1H), 5.63 (d, J = 10.1 Hz, 1H), 1.41+ (s, 3H), 1.41− (s, 3H). ^{13}C NMR (67.7 MHz, $CDCl_3$): δ 151.4, 131.9, 128.5, 125.8, 125.3, 122.5, 121.4, 117.5, 76.5, 27.8, 27.8. IR (neat, thin layer): 2978, 1481, 1427, 1383, 1364, 1267, 1211, 1198, 1167, 1126, 1111, 1082, 961, 876, 818, 775, 764 cm^{-1}. Anal. Calcd for $C_{11}H_{11}OCl$: C, 67.87; H, 5.70; Cl, 18.21. Found: C, 68.08; H, 5.65; Cl, 17.98.

6-Acetyl-2,2-dimethylchromene (19). A 1.00 g input of 4-hydroxyacetophenone produced 957 mg of **19** (64% yield) as a clear, colorless oil after purification by column chromatography (silica gel; hexanes:EtOAc, 95:5). ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.86 (dd, J = 8.2 and 2.4 Hz, 1H), 7.73 (d, J = 2.4 Hz, 1H), 6.90 (d, J = 8.2 Hz, 1H), 6.46 (d, J = 10.0 Hz, 1H), 5.78 (d, J = 10.0 Hz, 1H), 2.64 (s, 3H), 1.57+ (s, 3H), 1.57− (s, 3H). ^{13}C NMR (67.7 MHz, $CDCl_3$): δ 196.5, 157.3, 131.1, 130.2, 130.1, 126.8, 121.5, 120.5, 116.0, 77.4, 28.2, 28.2, 26.1. IR (neat, thin layer): 3050, 2978, 2928, 1676, 1642, 1603, 1572, 1489, 1464, 1435, 1385, 1370, 1319, 1273, 1213, 1188, 1169, 1134, 1121, 1111, 961, 934, 912, 880, 829, 772, 727 cm^{-1}. Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.10; H, 7.06.

6-Nitro-2,2-dimethylchromene (21). A 1.00 g input of 4-nitrophenol produced 973 mg of **21** (65% yield) as a yellow solid after purification by column chromatography (silica gel; hexanes:EtOAc, 95:5), mp 68−69 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 8.01 (dd, J = 8.8 and 2.9 Hz, 1H), 7.89 (d, J = 2.9 Hz, 1H), 6.81 (d, J = 8.8 Hz, 1H), 6.36 (d, J = 10.0 Hz, 1H), 5.75 (d, J = 10.0 Hz, 1H), 1.48+ (s, 3H), 1.48− (s, 3H). ^{13}C NMR (67.7 MHz, $CDCl_3$): δ 158.6, 141.3, 132.3, 125.1, 123.7, 121.9, 120.7, 116.4, 78.4, 28.4, 28.4. IR (KBr pellet): 2978, 1613, 1580, 1514, 1481, 1343, 1329, 1285, 1262, 1240, 1208, 1171, 1126, 1115, 1086, 964, 939, 899, 851, 829, 775, 766, 746, 704, 617 cm^{-1}. Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.74; H, 5.65; N, 6.56.

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