Synthesis of 4- and 6-Substituted 2,2-Dimethyl-2*H*-chromenes

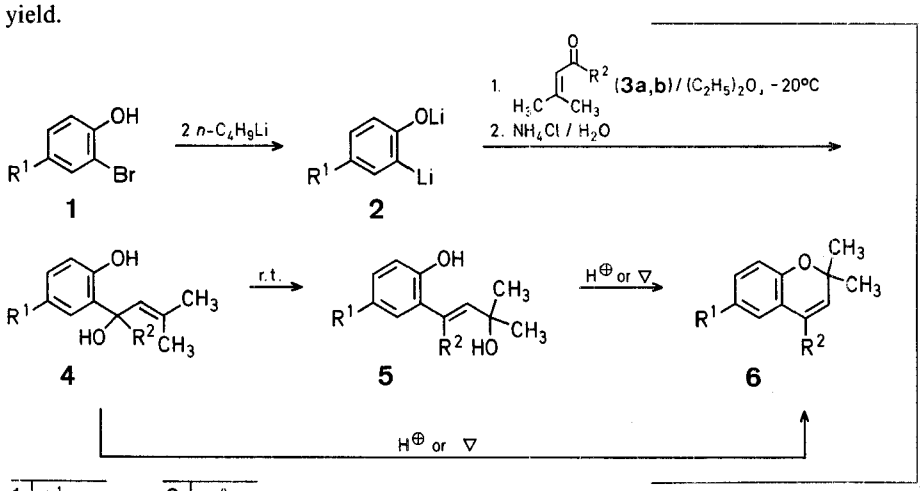
John J. TALLEY

Chemical Synthesis Branch, General Electric Corporate Research and Development Center, Schenectady, New York 12301, U.S.A.

Since the discovery that certain natural 2,2-dimethyl-2*H*-chromenes exhibit anti-juvenile hormone activity[1], there has been considerable interest in this class of compounds[2,3]. There are now several new methods for the preparation of chromene derivatives[4,5,6]. We now disclose the details of our new chromene synthesis which we feel will complement the published synthetic methods. Our method is simple, proceeds in good yield, and the isolation of intermediates is not necessary.

Treatment of an ethereal solution of *o*-bromophenol **(1a)** with 2.0 equivalents of *n*-butyllithium at room temperature for 2 h gave lithium *o*-lithiophenoxide **(2a)**[7]. This derivative was

cooled to −20°C and treated with an ethereal solution of either 3,3-dimethylacrolein **(3a)** or mesityl oxide **(3b)**. After an additional 10 min at −20°C the reaction was quenched by the addition of aqueous ammonium chloride solution to give the corresponding allylic alcohol **4** in nearly quantitative yield.

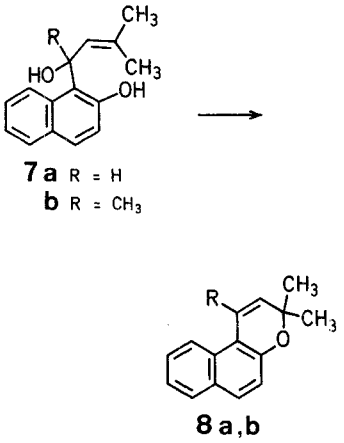


1	R^1
a	H
b	CH_3
c	OCH_3
d	Cl

3	R^2
a	H
b	CH_3

Upon standing at room temperature for any length of time, the initially formed allylic alcohols **4** rearranged to the more stable conjugated isomers **5**. The allylic rearrangement did not present a problem, as mixtures of **4** and **5** could be converted to the desired chromenes **6** upon treatment with a catalytic amount of acid. Attempted distillation of the intermediate allylic alcohol mixtures also resulted in cyclization to the corresponding chromenes **6**. Experimentally, we found it most advantageous to work up the crude allylic alcohol and then isolate the desired chromene by vacuum distillation. Attempted distillation of the *p*-chloroallylic alcohol **4da** resulted in extensive decomposition; only 20% of the desired chromene **6da** was isolated.

The dilithiated 1-bromo-2-naphthol reacted with 3,3-dimethylacrolein to produce the allylic alcohol **7a**. Noteworthy is the fact that chromene **8a** was formed in 90% yield when an ethereal solution of **7a** was allowed to stand over anhydrous magnesium sulfate. The trimethyl derivative **8b** was prepared in a similar manner.



This method is limited to those phenol derivatives that can be regioselectively *o*-brominated and that possess substituents compatible with organolithium reagents. The major advantages of this method are the ease of preparation and the availability of a number of *o*-bromophenols.

2,2,4,6-Tetramethyl-2*H*-chromene (6bb); Typical Procedure:

To a solution of 2-bromo-4-methylphenol (**1b**; 5.00 g, 0.027 mol) in anhydrous ether (80 ml) cooled to 0°C is added a 1.55 molar solution of *n*-butyllithium in hexane (34.5 ml, 0.054 mol) dropwise via syringe over a period of 20 min. The solution is allowed to warm to room temperature and maintained at that temperature for 2 h. The solution is cooled to −20°C, and mesityl oxide (**3b**; 2.94 g, 0.030 mol) in ether (40 ml) is added dropwise over 10 min. After stirring at −20°C for an additional 1 h, the mixture is treated with saturated aqueous ammonium chloride solution (10 ml). The phases were separated and the aqueous phase is extracted with ether (3 × 20 ml). The combined ether solution is dried with anhydrous magnesium sulfate, filtered, and concentrated to give an oil that is used in the next step without purification.

The crude diol is diluted with toluene (20 ml) and treated with *p*-toluenesulfonic acid (20 mg). An immediate exothermic reaction occurs

Table. 2,2-Dimethyl-2*H*-chromenes prepared

Product No.	R^1	R^2	Yield [%][a]	m.p. [°C] or b.p. [°C]/torr	Molecular formula[b] or Lit. data	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
6aa	H	H	75	84°/1.5	84°/1.5[9]	1.35 (s, 6H); 3.70 (s, 3H); 5.60 (d, 1H, J = 10 Hz); 6.27 (d, 1H, J = 10 Hz); 6.5–6.8 (m, 3H)
6ab	H	CH_3	85	63–65°/1.0	114–115°/17[10]	1.34 (s, 6H); 1.93 (d, 3H, J = 1.5 Hz); 5.3 (q, 1H, J = 1.5 Hz); 6.9 (m, 5H)
6bb	CH_3	CH_3	84	80–82°/0.4	$C_{13}H_{16}O$ (188.1)	1.35 (s, 6H); 1.95 (d, 3H, J = 1.5 Hz); 2.23 (s, 3H); 5.3 (q, 1H, J = 1.5 Hz); 6.75 (m, 3H)
6ca	OCH_3	H	70	77°/0.5	132–136°/15[11]	1.35 (s, 6H); 3.70 (s, 3H); 5.60 (d, 1H, J = 10 Hz); 6.27 (d, 1H, J = 10 Hz); 6.5–6.8 (m, 3H)
6cb	OCH_3	CH_3	70	120–121°/3.0	$C_{13}H_{16}O_2$ (204.1)	1.37 (s, 6H); 1.97 (d, 3H, J = 1.5 Hz); 3.77 (s, 3H); 5.5 (q, 1H, J = 1.5 Hz); 6.72 (s, 3H)
6da	Cl	H	20	100–105°/2.0	98°/1.0[12]	1.38 (s, 6H); 5.60 (d, 1H, J = 10 Hz); 6.20 (d, 1H, J = 10 Hz); 6.6–7.1 (m, 3H)
8a	H	—	90	80–82°	81–82°[13]	1.39 (s, 6H); 5.58 (d, 1H, J = 10 Hz); 6.93 (d, 1H, J = 10 Hz); 7.1–8.0 (m, 6H)
8b	CH_3	—	75	42–44°	oil[14]	1.38 (s, 6H); 2.31 (d, 3H, J = 1.5 Hz); 5.4 (q, 1H, J = 1.5 Hz); 6.7–8.2 (m, 6H)

[a] Yield of isolated product of ≥98% purity by G.L.C.

[b] Satisfactory microanalyses obtained: C ±0.23, H ±0.17.

and the solution becomes cloudy. The solution is stirred at 60°C for an additional 1 h and then the acid is neutralized by washing with excess saturated aqueous sodium hydrogen carbonate solution. The toluene solution is dried with anhydrous magnesium sulfate, filtered, and concentrated. The residue is distilled through a 15 cm glass helices packed column to give the product; yield: 4.19 g (84%); b.p. 80–82°C/0.4 torr.

2,2,4,6-Tetramethyl-2*H*-chromene can also be isolated by thermolysis of the crude allylic alcohol under vacuum, thereby eliminating the acid-catalyzed cyclization step.

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