Acylations of 2,2-Dimethyl-2*H*-chromenes

Seiji YAMAGUCHI, Satoru YAMAMOTO, Shoichi ABE, and Yoshiyuki KAWASE*
Department of Chemistry, Faculty of Science, Toyama University, Gofuku 3,190, Toyama 930
(Received June 22, 1983)

Orientation in acylation reactions of 2,2-dimethyl-2*H*-chromenes was studied. Five acetylchromenes were obtained with two methods and six formylchromenes were obtained with a third method. Demethylation of four acyl-methoxy-substituted chromenes gave the corresponding acylchromenols. 2,2-Dimethyl-2*H*-chromene-6-carboxylic acid (anofinic acid) was also obtained by oxidation of 6-formylchromene.

Many naturally occurring 2,2-dimethyl-2*H*-chromenes have an acetyl group in position 6 or 8.[1] But, the introduction of acetyl groups into 2,2-dimethyl-2*H*-chromenes has not been reported, because they were easily resinified with strong acids as acylating agents. We described a new preparative method of 2,2-dimethyl-2*H*-chromenes.[2] Now, we will report the acylation reactions of 2,2-dimethyl-2*H*-chromenes by using weak acids and their orientation. Acetylations were run in two methods; Method A: with acetic anhydride–zinc chloride in benzene at room temp for 3 h, at 80 °C for 20 min in a case of recovery, or at room temp for 1 h in a case that starting chromene was much resinified; Method B: with acetic acid–trifluoroacetic anhydride at room temp for 6 h. Formylations were run in a third method; Method C: with *N*-methylformanilide–phosphoryl chloride at 90 °C for 1 h. Their acylation yields are summarized in Table 1. In these reactions, both acetylations and formylations, similar orientations were observed (Chart 1). In all 2,2-dimethyl-2*H*-chromenes, except in 5-methoxy and 6-methoxy derivatives, the position 6 was the most reactive and the position 3, expected to be a styrene system, was not so reactive. 5-Methoxy derivative (**2**) afforded 8-formyl compound (para to methoxyl group) (**7b**), 6-methoxy derivative (**3**) afforded 7-acyl compounds (ortho to methoxyl group) (**8a, b**), and 8-methoxy derivative (**5**) gave a mixture of 5-acyl compounds (para to methoxyl group) (**10a, b**) and 6-acyl compounds (the most reactive position) (**11a, b**).

The structure of the acyl compounds were chiefly determined by the coupling constants of aromatic hydrogens in their ^{1}H-NMR spectra; other evidences are described below. 6-Acyl-2,2-dimethyl-2*H*-chro-

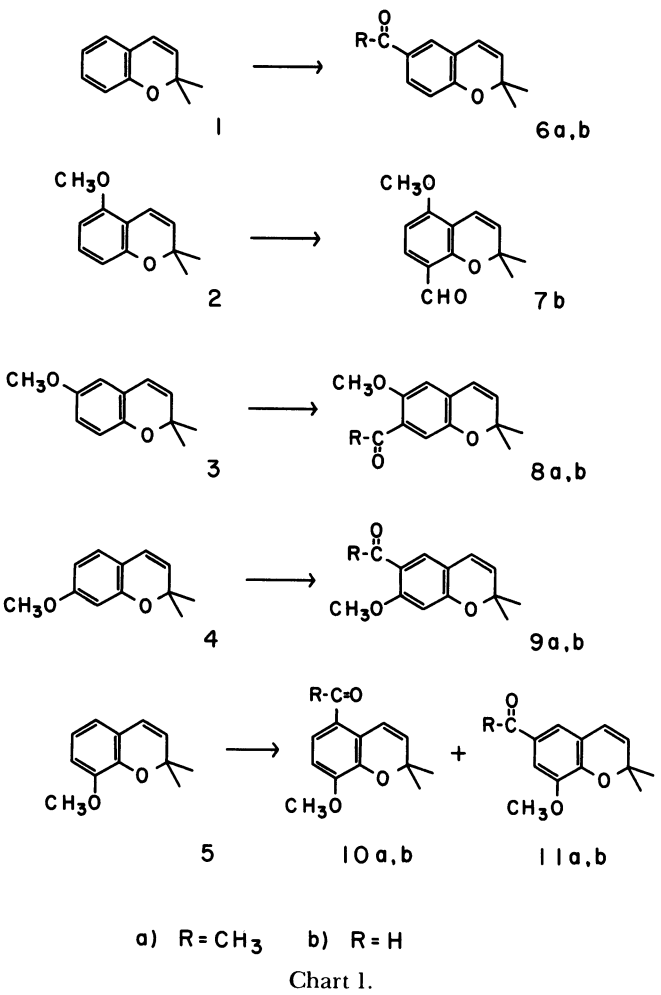


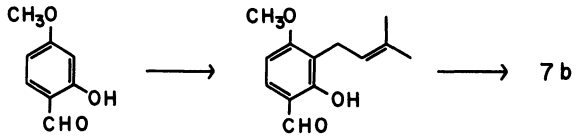
Chart 1.

Table 1. Acylations of 2,2-dimethyl-2*H*-chromenes

2,2-Dimethyl-2*H*-chromene	Acylated position	Yield/% Acetylation Method A	Acetylation Method B	Formylation Method C
1	6	64.3	64.4	39.6
2	8	0[a]	—	45.4
3	7	0[b] / 14.8[c]	35.5	51.9
4	6	8.5 / 25.4[d]	0[a]	55.3
5	5	9.7	8.2	38.2
	6	29.1	19.7	31.0

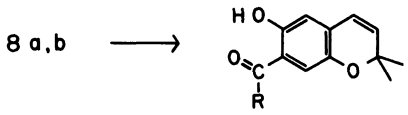
a) Only resin was obtained. b) Starting chromene was recovered. c) Acetylation was run at higher temp, 80 °C, for 20 min. d) Acetylation was run at room temp for a shorter period, 1 h.

menes (**6a ,b**) showed ortho and meta coupling in their ^{1}H-NMR spectra. There was no E.T. band due to a mesomery between C=O and C=C double bonds, such as 7-acylchromenes may show (Fig. 1). N. M. Venkama and R. G. S. Krishna reported the DDQ oxidation of 2,2,6-trimethyl-2*H*-chromene and 6-ethyl-2,2-dimethyl-2*H*-chromene to 6-formyl- and 6-acetyl-2,2-dimethyl-2*H*-chromene (**6a, b**).[3] Our compounds (**6a, b**) from 2,2-dimethyl-2*H*-chromene were identical with theirs which were obtained from the DDQ oxidation in their spectra. The structure of 8-formyl-5-methoxy-2,2-dimethyl-2*H*-chromene (**7b**) was assured by another synthetic method; dehydrogenetic cyclization of 2-hydroxy-4-methoxy-3-(3-methyl-2-butenyl)-benzaldehyde (**13**) to **7b**(Chart 2). The ^{1}H-NMR spectra of 5-acyl compounds (**10a, b**) showed two doublets with 9—10 Hz ortho coupling and deshielding by 5-acyl groups at 4-H proton.

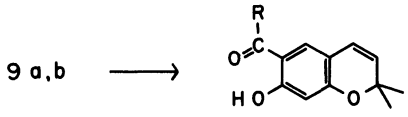


12 13

Chart 2.



14 a,b



15 a,b

Chart 3.

Phosphoryl chloride is a weaker acid than zinc chloride or trifluoroacetic acid (derived from trifluoroacetic anhydride). Therefore, formylations could be run at higher temperatures than acetylations, and

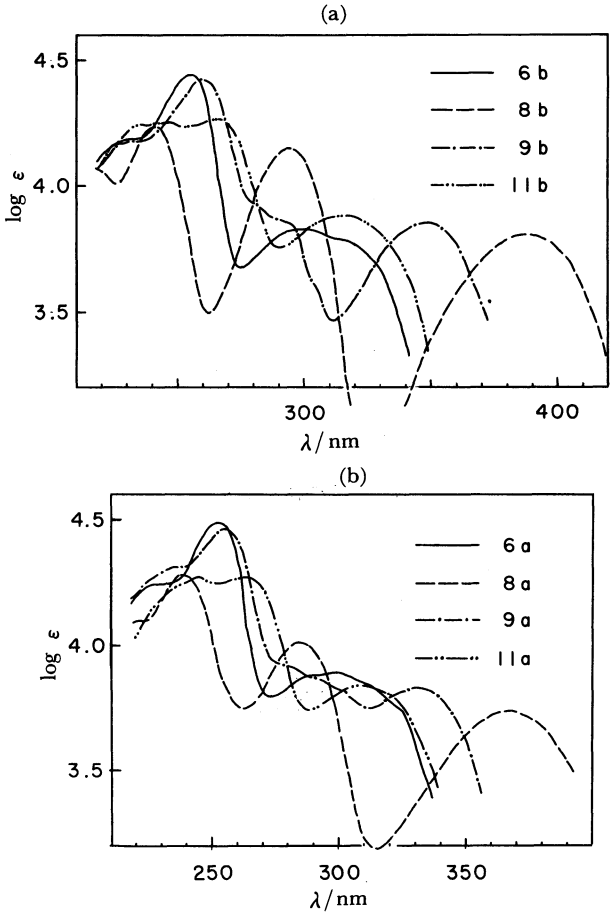
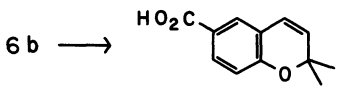


Fig. 1. (a) UV spectra of acetylchromenes, (b) UV spectra of formylchromenes.



16

Chart 4.

Table 2. ^{1}H-NMR data of acylated chromenes

	2-H	3-H	4-H	5-H	6-H	7-H	8-H
6a	1.4 s	5.5 d(10)	6.2 d(10)	7.5 d(2)	2.4 s	7.6 dd(8+2)	6.6 d(8)
8a	1.3 s	5.6 d(10)	6.2 d(10)	6.4 s	3.8 s	2.4 s	7.0 s
9a	1.4 s	5.4 d(9)	6.2 d(9)	7.4 s	2.4 s	3.8 s	6.2 s
10a	1.4 s	5.6 d(10)	7.2 d(10)	2.4 s	7.2 d(9)	6.6 d(9)	3.8 s
11a	1.4 s	5.5 d(10)	6.2 d(10)	7.1 or 7.3 d(2)	2.4 s	7.1 or 7.3 d(2)	3.8 s
6b	1.5 s	5.8 d(10)	6.6 d(10)	7.7 d(2)	10.9 s	7.8 dd(8+2)	7.0 d(8)
7b	1.5 s	5.7 d(10)	6.7 d(10)	4.0 s	6.6 d(9)	7.6 d(9)	10.6 s
8b	1.4 s	5.9 d(10)	6.4 d(10)	6.6 s	4.0 s	10.5 s	7.3 s
9b	1.5 s	5.6 d(10)	6.5 d(10)	7.6 s	10.5 s	4.0 s	6.5 s
10b	1.6 s	7.3 d(10)	7.8 d(10)	10.3 s	8.1 d(11)	6.2 d(11)	4.2 s
11b	1.5 s	5.7 d(11)	6.4 d(11)	7.2 or 7.4 d(2)	10.0 s	7.2 or 7.4 d(2)	4.0 s

Chemical shifts: δ, in CCl_4 (Coupling constants: J/Hz).

formylations gave better yields than acetylations in all methoxy-substituted 2,2-dimethyl-2*H*-chromenes. Acetylations of 5-methoxy-2,2-dimethyl-2*H*-chromene (**2**) and 7-methoxy-2,2-dimethyl-2*H*-chromene (**4**) gave mainly resin. This result shows that the methoxyl group in 5- or 7-position enhanced the electron density in the C=C double bond and labilized 2*H*-chromenes against acids. The acetylations of 5,7-dimethoxy-2,2-dimethyl-2*H*-chromene to 6-acetyl-5,7-dimethoxy-2,2-dimethyl-2*H*-chromene (methylevodionol) or 8-acetyl-5,7-dimethoxy-2,2-dimethyl-2*H*-chromene (methylalloevodionol), as we would suppose, gave only resin.

The spectral data of **9a** and **11a** agreed with the reported data of natural methyleupariochromene[4] (encecalin[5]) and acetovanillochromene.[6] Demethylation reactions of **8a, b** and **9a, b** with anhydrous magnesium iodide gave the corresponding chromenols (**14a, b** and **15a, b**) (Chart 3); the spectral data of **15a** agreed with the reported data of natural eupariochromene.[4] Oxidation of **6b** with silver oxide gave 2,2-dimethyl-2*H*-chromene-6-carboxylic acid (**16**) (Chart 4), and its spectral data agreed with the reported data of natural anofinic acid.[7]

Experimental

The boiling points and melting points were uncorrected (in boiling points: 1 mmHg ≈133.322 Pa). The IR, UV, and ^{1}H-NMR spectra were measured on a Hitachi EPI-S2 spectrophotometer, a Hitachi 124 spectrophotometer, and a JEOL JNM-MH-60 spectrometer, respectively.

*Acetylations of 2,2-Dimethyl-2*H*-chromenes. Method A*: To a mixture of 2,2-dimethyl-2*H*-chromenes (10 mmol), zinc chloride (3.4 g, 25 mmol), and dry benzene (5 mL) was added acetic anhydride (1.0 g, 10 mmol) over a 20 min period. The mixture was stirred at room temp for 3 h, at 80 °C for 20 min, or at room temp for 1 h. After the reaction, the mixture was treated with 10% hydrochloric acid and then extracted with ether. The combined ether extracts was washed with 5% sodium hydroxide solution, and dried over anhydrous sodium sulfate. After the removal of the ether, the resultihg oil was distilled to give acetylchromenes.

Method B: Under cooling in an ice-water bath, trifluoroacetic anhydride (4.2 g, 20 mmol) was added to a solution of 2,2-dimethyl-2*H*-chromenes (10 mmol) in acetic acid (1.2 g, 20 mmol). The mixture was then allowed to stand for 6 h at room temp. After the reaction, the mixture was treated with ice water, and alkalified with aqueous sodium hydrogencarbonate solution, and then extracted with ether. The ether extracts were dried over anhydrous sodium sulfate. After the removal of the ether, the resulting oil was distilled to give acetylchromenes.

*Formylations of 2,2-Dimethyl-2*H*-chromenes. Method C*: To a mixture of *N*-methylformanilide (30 g, 20 mmol) and phosphoryl chloride (4.4 g, 10 mmol), 2,2-dimethyl-2*H*-chromenes (10 mmol) were added. The mixture was then heated at 90 °C for 1 h with stirring. After cooling, the mixture was boiled with an aqueous sodium hydroxide solution (1.5 g, in 15 mL) for 1 min and then extracted with ether. The ethereal layer was washed with 10% hydrochloric acid and 5% sodium hydroxide solution, and then dried over anhydrous sodium sulfate. After the removal of the ether, the resulting oil was distilled to give formyl 2,2-dimethyl-2*H*-chromenes.

In case of the acylations of **5**, mixtures were obtained. These were separated into components, 5-acyl compounds (**10a, b**) and 6-acyl compounds (**11a, b**) by silica-gel chromatography. The yields and ^{1}H-NMR data of acyl chromenes are summarized in Tables 1 and 2, and some UV data are shown in Figs. 1a and 1b. Some other physical data are listed below.

6a, Bp 126—130 °C(4 mmHg); IR (neat): 1675 cm^{-1}.[3] **8a**, Bp *ca.* 126 °C (3 mmHg) (bath temp); mp 67—68.5 °C; IR (KBr disk): 1670 cm^{-1}; Found: C, 70.62; H, 6.67%. Calcd: C, 72.39; H, 6.94%. **9a**, Bp *ca.* 146 °C (2 mmHg) (bath temp); IR (neat): 1665 cm^{-1}; Found: C, 72.15; H, 6.93%. Calcd: C, 72.39; H, 6.94%. **10a**, Benzene-hexane eluted fractions; mp 85.5—87.5 °C (recrystallized from hexane); IR (KBr disk): 1665 cm^{-1}; UV (EtOH): 253 (log ε 4.36), 285 (4.06), 340 nm (3.60); Found: C, 72.29; H, 6.99%. Calcd: C, 72.39; H, 6.94%. **11a**, Benzene-hexane eluted fractions; mp 73—73.5 °C (recrystallized from hexane); IR (KBr disk): 1670 cm^{-1}; Found: C, 72.37; H, 6.94%. Calcd: C, 72.39; H, 6.94%. **6b**, Bp 95—103 °C (2 mmHg); IR (KBr disk): 1685 cm^{-1}.[3] **7b**, Benzene-hexane eluted fractions; bp 175—180 °C (23 mmHg); IR (neat): 1680 cm^{-1}; UV (EtOH): 264 (log ε 4.24), 277 (4.16), 291 nm (4.14); Found: C, 71.82; H, 6.46%. Calcd: C, 71.54; H, 6.47%. **8b**, Mp 87—88 °C (recrystallized from ether); IR (KBr disk): 1670 cm^{-1}; Found: C, 71.65; H, 6.52%. Calcd: C, 71.54; H, 6.47%. **9b**, Bp 130—133 °C (2 mmHg); mp 71.5—73 °C (recrystallized form cyclohexane); IR (KBr disk): 1675 cm^{-1}; Found; C, 71.29; H, 6.47%. Calcd:C, 71.54; H, 6.47%. **10b**, Benzene eluted fractions; bp 129—140 °C (5 mmHg) (bath temp); IR (neat): 1675 cm^{-1}; UV (EtOH); 252 (log ε 4.19), 293 (4.03), 347 nm (3.51); Found: C, 71.32; H, 6.57%. Calcd: C, 71.54; H, 6.47%. **11b**, Benzene eluted fractions; bp 135—150 °C (5 mmHg) (bath temp); IR (neat): 1680 cm^{-1}; Found: C, 71.29; H, 6.48%. Calcd: C, 71.54; H, 6.47%

Another Preparative Method of 7b. To a solution of 2-hydroxy-5-methoxybenzaldehyde (**12**) (2.5 g, 16.4 mmol) in dry benzene (20 mL) was added sodium hydride (53% dispersed in mineral oil; 1.5 g) and 4-bromo-2-methyl-2-butene (2.5 g, 16.8 mmol). The mixture was refluxed overnight. After the reaction, the mixture was poured into 10% hydrochloric acid, and the separated benzene layer was dried over anhydrous sodium sulfate. Removal of the benzene gave an oily residue, which was chromatographed on a silica-gel column. The benzene eluted fractions gave 2-hydroxy-4-methoxy-3-(3-methyl-2-butenyl)benzaldehyde (**13**) (217 mg, 5.8%); IR (neat): 1645 cm^{-1}; ^{1}H-NMR (CCl_4): δ=1.6 (3H, broad s), 1.7 (3H, broad s), 3.3 (2H, d, J=7 Hz), 3.9 (3H, S), 5.1 (1H, broad t, J=7 Hz), 6.5 (1H, d, J=9 Hz), 7.3 (1H, d, J=9 Hz), 9.7 (1H, s), 11.4 (1H, s). To a solution of **13** (150 mg, 0.681 mmol) in dry benzene (70 mL), DDQ (170 mg, 0.749 mmol) was added. This mixture was then refluxed for 1 h. After cooling, the mixture was filtered. The filtrate was washed with 5% sodium hydroxide solution and saturated sodium chloride aqueous solution and dried over anhydrous sodium sulfate. After removal of the benzene, the resulting oil was chromatographed on a silica-gel column. The benzene eluted fractions gave **7b** (26 mg, 17.5%). The IR and ^{1}H-NMR spectra were identical with those of **7b** from **2**.

Demethylations of 8a, b and 9a, b. In dry benzene (5 mL) and anhydrous ether (2 mL), magnesium metal (0.2 g, 8.2 mmol) was treated with iodine (1.1 g, 8.7 mmol). The mixture was slightly heated while stirring until the color disappeared. To this mixture was then added a solution of **8a, b** or **9a, b** (5 mmol) in dry benzene (10 mL). and the mixture was refluxed for 3 h with stirring. After cooling, the mixture was treated with 10% hydrochloric acid and then extracted with benzene. The benzene layer was washed with water and dried over anhydrous sodium sulfate. After removal of the benzene, the resulting oil was chromatographed on a silica-gel column . The benzene eluted fractions gave corresponding chromenols (**14a, b** or **15a, b**). **14a**, Yield:

22.1%; mp 66—68 °C (recrystallized from hexane); IR (KBr disk): 1645 cm^{-1}; UV (EtOH): 238 (log ε 4.26), 294 (4.14), 388 nm (3.68); ^{1}H-NMR (CCl_4): δ=1.4 (6H, s), 2.5(3H, s), 5.8(1H, d, J=10 Hz), 6.2 (1H, d, J=10 Hz), 6.6 (1H, s), 7.1 (1H, s), 11.8 (1H, s); Found: C, 71.63; H, 6.57%. Calcd: C, 71.54: H, 5.47%. **14b**, Yield: 20.4%; mp 97—99 °C (recrystallized from hexane); IR (KBr disk): 1645 cm^{-1}; UV (EtOH): 239 (log ε 4.23), 294 (4.16), 391 nm (3.76); ^{1}H-NMR (CCl_4): δ=1.5 (6H, s), 5.9 (1H, d, J=10 Hz), 6.4 (1H, d, J=10 Hz), 6.6 (1H, s), 7.0 (1H, s), 10.0 (1H, s), 10.8 (1H, s); Found: C, 70.68; H, 5.91%. Calcd: C, 70.57; H, 5.92%. **15a**, Yield: 43.9%; mp 72—73.5 °C (recrystallized from hexane); IR (KBr disk): 1655 cm^{-1}; UV (EtOH): 227 sh (log ε 4.16), 234 (4.27), 257 (4.54), 291 sh (3.81), 347 nm (3.79); ^{1}H-NMR (CCl_4); δ=1.5 (6H, s), 2.6 (3H, s), 5.7 (1H, d, J=10 Hz), 6.5 (1H, d, J=10 Hz), 6.5 (1H, s), 7.5 (1H, s), 13.2 (1H, s); Found: C, 71.32; H, 6.39%. Calcd: C, 71.54; H, 6.47%. **15b**, Yield: 54.2%; mp 97—99 °C (recrystallized from cyclohexane); IR (KBr disk): 1635 cm^{-1}; UV (EtOH): 228 sh (log ε 4.16), 235 (4.24), 259 (4.48), 282 sh (3.87), 293 sh (3.82), 349 nm (3.74); ^{1}H-NMR (CCl_4); δ=1.4 (6H, s), 5.5 (1H, d, J=10 Hz), 6.2 (1H, d, J=10 Hz), 6.2 (1H, s), 7.0 (1H, s), 9.6 (1H, s), 12.9 (1H, s); Found: C, 70.49; H, 5.87%. Calcd: C, 70.57; H, 5.92%.

*Oxidation of **6b** to Anofinic Acid.* To a solution of silver nitrate (2.3 g, 14.0 mmol) in water (20 mL), sodium hydroxide (1.0 g) was added. To this silver oxide suspension, a solution of **6b** (1.2 g, 6.38 mmol) in ethanol (20 mL) was added. The mixture was then refluxed for 2 h. After the reaction, the mixture was filtered. The filtrate was washed with ether and then acidified with 10% hydrochloric acid. The crystals thus obtained were collected and recrystallized from benzene-hexane (1 : 9) to give **16** (770 mg, 59.4%); mp 158.5—160 °C; IR (KBr disk): 1675 cm^{-1}; UV (EtOH): 239.5 (log ε 4.68), 280.5 (3.88), 306 (3.78), 318 nm (3.67); ^{1}H-NMR (CCl_4): δ=1.5 (6H, s), 5.8 (1H, d, J=10 Hz), 6.5 (1H, d, J=10 Hz), 7.0 (1H, d, J=9 Hz), 7.9 (1H, d, J=2 Hz), 8.1 (1H, dd, J=9+2 Hz), 10.3 (1H,s); Found: C, 70.75; H, 5.85%. Calcd: C, 70.57; H, 5.92%.

References

1) G. P. Ellis, "Chromenes, Chromanones, and Chromones," Wiley, New York, N. Y. (1976), p. 43.

2) Y. Kawase, S. Yamaguchi, H, Horita, J, Takeno, and H. Kameyama, *Bull. Chem. Soc. Jpn.*, **55**, 1153 (1982).

3) N. M. Venkama and R. G. S. Krishna, *Synthesis*, **1979**, 144; *Indian J. Chem.*, **17B**, 73 (1979).

4) T. Anthonsen, *Acta Chem. Scand.*, **23**, 3605 (1969).

5) L. F. Bjeldames and T. A. Geisman, *Phytochemistry*, **8**, 1293 (1969).

6) D. R. Taylor and J. A. Wright, *Phytochemistry*, **10**, 1665 (1971).

7) K. Shima, S. Hisada, and I. Inagaki, *Yakugaku Zasshi*, **91**, 1124 (1971).