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Synthesis of 5-(Substituted methyl)-6,8-dimethyl-4-chromanones[1)]

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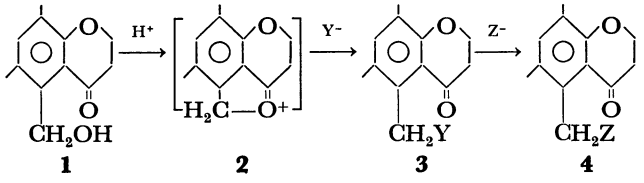
Synopsis. 5-(Substituted methyl)-6,8-dimethyl-4-chromanones were synthesized from the reactions of 5-hydroxymethyl-6,8-dimethyl-4-chromanone with nucleophilic reagents in acid media, and the reactions of its 5-halomethyl derivatives with ethoxide or phenoxide nucleophiles.

In previous papers,[2)] polymers having 4-chromanones have been synthesized since 4-chromanones are useful ultraviolet absorbers.

In this paper, the syntheses of 5-(substituted methyl)-6,8-dimethyl-4-chromanones from the reactions of 5-hydroxymethyl-6,8-dimethyl-4-chromanone(**1**) with nucleophilic reagents in the presence of acid catalysts are presented. In addition, 5-(substituted methyl)-6,8-dimethyl-4-chromanones have been prepared from 5-halomethyl derivatives of **1**.



1 **2** **3** **4**

3a Y=Cl-
3b Y=Br-
3c Y=CH_3O-
3d Y=C_2H_5O-
3e Y=HO-⟨○⟩-
3f Y=(OH, H_3C)⟨○⟩-
3g Y=(OH, ×)⟨○⟩-
3h Y=HO-(×,×)⟨○⟩-
3i Y=⟨○⟩-S-
3j Y=H_3C-⟨○⟩-S-
4d Z=C_2H_5O- (from **3b**)
4k Z=⟨○⟩-O- (from **3a**)
4m Z=H_3C-⟨○⟩-O- (from **3a**)

×=*t*-Bu-

Results and Discussion

*Reactions of **1** with Nucleophilic Reagents.* The reactions of **1** with nucleophilic reagents in acidic media were carried out and reaction conditions are shown in Table 1.

The chlorination of **1** in dioxane solution in the presence of hydrochloric acid as the catalyst and nucleophilic reagent gave 5-chloromethyl-6,8-dimethyl-4-chromanone(**3a**). Similarly, the bromination of **1** in dioxane in the presence of hydrobromic acid afforded 5-bromomethyl-6,8-dimethyl-4-chromanone(**3b**). The methanolysis of **1** in a mixture of methanol and dioxane with perchloric acid as the catalyst gave 5-methoxymethyl-6,8-dimethyl-4-chromanone(**3c**). The ethanolysis of **1** in ethanol in the presence of perchloric acid gave 5-ethoxymethyl-6,8-dimethyl-4-chromanone(**3d**).

The reactions of **1** with phenol and *p*-cresol in ethanol gave 5-(4-hydroxybenzyl and 2-hydroxy-5-methylbenzyl)-6,8-dimethyl-4-chromanones(**3e** and **3f**), respectively. The reaction of **1** with *p*-cresol gave a mixture of **3f** and **3d** in the mole ratio of 8:9, which was measured by the peak area in the ^{1}H-NMR spectrum. The low yield of **3f** is due to the lower fractionation of **3f** from the reaction mixture. When a mixed solution of dioxane and ethanol was used, the reaction gave **3f** along with a small amount of resinous product. No formation of **3d** was detected. With increasing ratio of dioxane to ethanol, the resinous product increased. When dioxane solvent was used solely in the reaction of **1** with *p*-cresol, phenol, and *p*-*t*-butylphenol, 5-substituted methyl compounds were not isolated from the reaction mixtures. It was found that the reaction was affected markedly by the character of the solvents, dioxane causing a remarkable effect in the yield of products.

The reaction of **1** with excess 2,6-di-*t*-butylphenol in dioxane gave 5-(4-hydroxy-3,5-di-*t*-butylbenzyl)-6,8-dimethyl-4-chromanone(**3h**).

Thiophenol and *p*-thiocresol gave 5-phenylthiomethyl and 5-(*p*-tolylthiomethyl) compounds(**3i** and **3j**), respectively, in larger yields than in the cases of phenol and *p*-cresol.

The results shown in Table 1 indicate that the yield of the products are largely dependent on the nucleophilicity[3)] of reagents and the stability of the oxonium ion(**2**)[1)] in acidic solvents.

*Synthesis of **4d**, **4k**, and **4m** from 5-Halomethyl Derivatives (**3a** and **3b**).* The reaction of **3b** with sodium ethoxide gave **4d** quantitatively, but the use of **3a** under similar conditions gave the starting material. The reactions of **3a** with phenol and *p*-cresol gave 5-phenoxymethyl and 5-(*p*-tolyloxymethyl) derivatives (**4k** and **4m**), respectively.

Experimental

Melting points are uncorrected. IR spectra were obtained using KBr pellets in a Hitachi EPI-G2 spectrophotometer. ^{1}H-NMR spectra were recorded on a JEOR Model PS-100 spectrometer with tetramethylsilane as the internal standard. Mass spectra were obtained on a Hitachi RUM-6 mass spectrometer operating at 70 eV.

Materials. **1** was prepared by the reported method,[1)] mp 95—97 °C [lit,[1)] mp 95—97 °C].

*Reactions of **1** with Nucleophilic Reagents.* The following procedure for the preparation of 5-(substituted methyl)-6,8-dimethyl-4-chromanone is representative.

A mixture of **1** and hydrochloric acid in dioxane was stirred at 80 °C for 6 h. After completion of the reaction, the reaction mixture was poured into water, and then extracted with chloroform. The chloroform layer was washed

Table 1. Reactions of 5-hydroxymethyl-6,8-dimethyl-4-chromanone with nucleophilic reagents

Reaction conditions: temp; 80 °C, time; 6 h, catalysts; HCl=hydrochloric acid(36%), HBr=hydrobromic acid(47%), $HClO_4$=perchloric acid(70%)

Reactant (mmol) 1	Phenols		Catalyst (ml)		Solvent (ml)		Product	Yield (%)
5.0			HCl	10.0	Dioxane	35.0	**3a**	83.2
5.0			HBr	10.0	Dioxane	35.0	**3b**	81.4
5.0[a]			$HClO_4$	10.0	MeOH Dioxane	10.0 35.0	**3c**	70.0
5.0			$HClO_4$	10.0	EtOH	35.0	**3d**	57.2
5.0	Phenol	10.0	$HClO_4$	10.0	EtOH	35.0	**3e**	5.0
5.0	*p*-Cresol	10.0	$HClO_4$	10.0	EtOH	35.0	**3f**	5.4
1.0	*p*-Cresol	2.0	$HClO_4$	2.0	EtOH Dioxane	5.0 2.0	**3f**	27.0
1.0	*p*-Cresol	2.0	$HClO_4$	2.0	EtOH Dioxane	1.0 6.0	**3f**	20.3
5.0	*p*-Cresol	10.0	$HClO_4$	10.0	Dioxane	35.0	—	—
5.0	*p*-*t*-Butylphenol	10.0	$HClO_4$	10.0	EtOH	35.0	**3g**	11.8
5.0[b]	2,6-di-*t*-Butylphenol	25.0	$HClO_4$	0.5	Dioxane	6.0	**3h**	22.4
5.0	Thiophenol	10.0	$HClO_4$	10.0	EtOH	35.0	**3i**	24.2
2.5	*p*-Thiocresol	5.0	$HClO_4$	5.0	EtOH	17.5	**3j**	28.2

a) Temp: 60 °C, Time: 4 h. b) Time: 4 h.

with aqueous sodium hydroxide and water, successively. After removal of the solvent, the residue was recrystallized to give the 5-chloromethyl derivative.

3a: Mp 102—104 °C (from ligroin). IR: 1665(C=O), 690 cm^{-1} (C–Cl). NMR($CDCl_3$): δ=2.14(3H, s), 2.30(3H. s), 2.79(2H, t), 4.45(2H, t), 5.11(2H, s), 7.12(1H, s). MS: *m/e* 226(M^+), 189(M^+-Cl). Found: C, 64.19; H, 5.86%. Calcd for $C_{12}H_{13}O_2Cl$: C, 64.15; H, 5.83%.

3b: Mp 118—120 °C (from ligroin). IR: 1670(C=O), 542 cm^{-1} (C–Br). NMR(CCl_4): δ=2.14(3H, s), 2.28(3H, s), 2.73(2H, t), 4.46(2H, t), 5.03(2H, t), 7.05(1H, s). MS: *m/e* 270(M^+), 189(M^+-Br). Found: C, 53.56; H, 4.88%. Calcd for $C_{12}H_{13}O_2Br$: C, 53.55; H, 4.87%.

3c: Mp 47 °C (from petroleum ether). IR: 2810(O–CH_3), 1680 cm^{-1} (C=O). NMR(CCl_4): δ=2.11(3H, s), 2.23 (3H, s), 2.65(2H, t), 5.27(3H, s), 4.38(2H, t), 4.72(2H, s), 6.98 (1H, s). MS: *m/e* 220(M^+), 205(M^+-CH_3). Found: C, 70.91; H, 7.19%. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32%.

3d: Mp 70 °C (from petroleum ether). IR: 2800(O–C_2H_5), 1678 cm^{-1} (C=O). NMR(CCl_4): δ=1.14(3H, t), 2.13(3H, s), 2.27(3H, s), 2.71(2H, t), 3.48(2H, q), 4.44 (2H, t), 4.78(2H, s), 7.00(1H, s) MS: *m/e* 234(M^+), 205 ($M^+-C_2H_5$). Found: C, 71.78; H, 7.76%. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74%.

3e: Mp 215—216 °C (from benzene). IR: 3275(OH), 1658 cm^{-1} (C=O). NMR(DMSO-d_6): δ=2.05(3H, s), 2.13 (3H, s), 2.72(2H, t), 4.31(2H, s), 4.45(2H, t), 6.64(4H, q), 7.12(1H, s), 9.02(1H, s). MS: *m/e* 282(M^+), 266(M^+-H_2O), 189(M^+—PhOH). Found: C, 76,48; H, 6.14%. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.42%.

3f: Mp 164—166 °C (from ligroin). IR: 3275(OH), 1660 cm^{-1} (C=O). NMR(CCl_4): δ=2.11(3H, s), 2.15(3H, s), 2.20(3H, s), 2.73(2H, t), 4.18(2H, s), 2.42(2H, t), 6.34 (1H, s), 6.47(1H, d), 6.59(1H, d), 6.67(1H, dd), 7.08(1H, s). MS: *m/e* 296 (M^+), 281(M^+-CH_3), 278(M^+-H_2O), 189(M^+—MePhOH). Found: C, 76.89; H, 6.83%. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80%.

3g: Mp 135—136 °C (from ligroin). IR: 3250(OH), 1660 cm^{-1} (C=O). NMR(CCl_4): δ=1.18(9H, s), 2.15(3H, s), 2.20(3H, s), 2.77(2H, t), 4.20(2H, s), 4.40(2H, t), 6.60(1H, d), 6.75(1H, s), 6.77(1H, d), 6.93(1H, dd), 7.08 (1H, s). MS: *m/e* 338(M^+), 323(M^+-CH_3), 189(M^+—*t*-BuPhOH). Found: C, 78.99; H, 7.75%. Calcd for $C_{22}H_{26}O_3$: C, 78.07; H, 7.75%.

3h: Mp 200—203 °C (from ligroin). IR: 3620(OH), 1670 cm^{-1} (C=O). NMR($CDCl_3$): δ=1.35(18H, s), 2.17 (3H, s), 2.19(3H, s), 2.74(2H, t), 4.41(2H, t), 4.41(2H, s), 4.88(1H, s), 6.82(2H, s), 7.11(1H, s). MS: *m/e* 394(M^+), 379(M^+-CH_3), 337(M^+—*t*-Bu), 189(M^+—*t*-Bu_2PhOH). Found: C, 78.94; H, 8.79%. Calcd for $C_{26}H_{34}O_3$: C, 79.15; H, 8.69%.

3i: Mp 98—99 °C (from ligroin). IR: 1650 cm^{-1} (C=O). NMR(CCl_4): δ=2.12(3H, s), 2.16(3H, s), 2.60(2H, t), 4.35(2H, t), 4.61(2H, s), 6.98—7.36(6H, m). MS: *m/e* 298(M^+), 189(M^+—PhS). Found: C, 72.90; H, 6.17%. Calcd for $C_{18}H_{18}O_2S$: C, 72.45; H, 6.08%.

3j: Mp 93—95 °C (from ligroin). IR: 1670 cm^{-1} (C=O). NMR(CCl_4): δ=2.13(6H, s), 2.30(3H, s), 2.60(2H, t), 4.35(2H, t), 4.55(2H, s), 6.98(1H, s), 7.06(4H, q). MS: *m/e* 312(M^+), 189(M^+—MePhS). Found: C, 73.51; H, 6.31%. Calcd for $C_{19}H_{20}O_2S$: C, 73.04; H, 6.45%.

4k: A mixture of phenol (0.26 g, 2.8 mmol) and sodium (0.07 g, 3.0 mmol) in ethanol (20 ml) was stirred for 2 h at 80 °C. **3a**(0.56 g, 2.5 mmol) was then added to the solution and refluxed for 4 h. The resulting sodium chloride was removed by filtration, filtrate condensed and recrystsallized from ligroin to give **4k**; yield 0.11 g, mp 152—154 °C. IR: 1670 cm^{-1} (C=O). NMR(CCl_4): δ= 2.17(3H, s), 2.29(3H, s), 2.70(2H, t), 4.43(2H, t), 5.41(2H, s), 6.72—7.23(6H, m). MS: *m/e* 282(M^+), 189(M^+—PhO). Found: C, 76.33; H, 6.58%. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.42%.

4m: *p*-Cresol (0.30 g, 2.8 mmol) was treated with sodium (0.07 g, 3.0 mmol), **3a** (0.56 g, 2.5 mmol), and ethanol (20 ml) essentially as described in the preparation of **4k**. The product was recrystallized from ligroin to give **4m**; yield 0.10 g, mp 164—166 °C. IR: 1675 cm^{-1} (C=O). NMR(CCl_4): δ=2.16(3H, s), 2.25(3H, s), 2.28 (3H, s), 2.69(2H, t), 4.42(2H, t), 5.36(2H, s), 6.40—7.24(4H, m), 7.06(1H, s), MS: *m/e* 296(M^+), 189(M^+—MePhO). Found: C, 76.68; H, 6.98%. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80%.

Synthesis of ***4d*** *from* ***3b***. **3b**(0.28 g, 1.0 mmol) was added slowly to ethanol (10 ml) containing sodium ethoxide (0.078 g, 1.5 mmol). The solution was stirred at 80 °C for 2 h, and the solvent removed under reduced pressure. The residue was dissolved in ligroin and filtered off. The filtrate was evaporated to dryness under reduced pressure to give **4d**; yield 0.22 g, mp 70 °C, after recrystallization from ligroin.

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