Aldol Condensation of 6-Alkoxy-2,2-dimethylchroman-4-ones with Substituted Benzaldehydes Using Tetramethylorthosilicate and Potassium Fluoride

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The aldol condensation of 6-alkoxy-2,2-dimethylchromanones **1** or **2** with substituted benzaldehydes in the presence of tetramethylorthosilicate and potassium fluoride affords 6-alkoxy-3-benzylidene-2,2-dimethylchromanones **5-10** while other conventional methods were unsuccessful.

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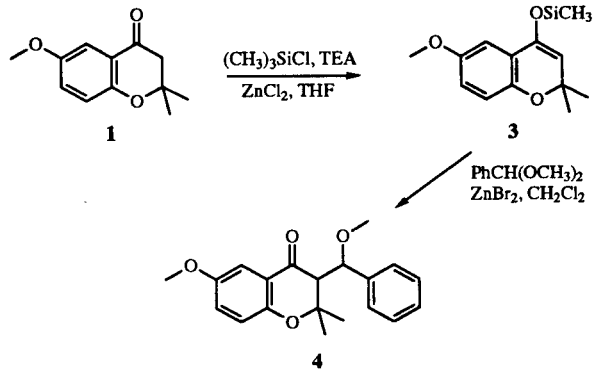
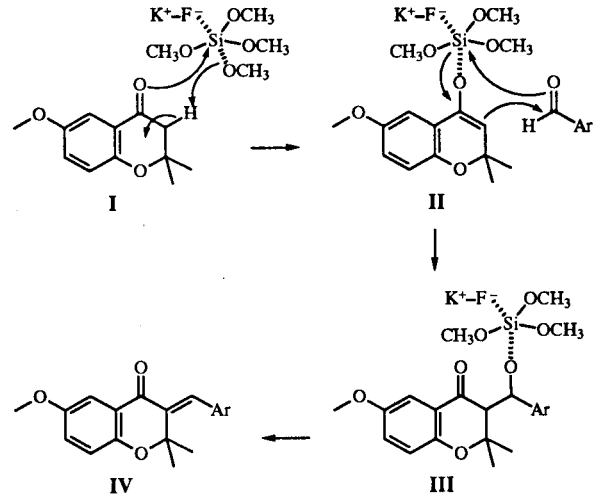
6-Alkoxy-2,2-dimethylchroman-4-ones are important intermediates in the synthesis of 6-hydroxy-2,2-dimethylchrom-3-ene which possess antitumor and antimutagenic activity [1]. During the course of our research we wished to prepare analogs of 6-alkoxy-2,2-dimethylchroman-4-ones which possess a 3-benzylidene group. Such derivatives were thought to be readily accessible by aldol condensation of chromanones **1** or **2** with a substituted benzaldehyde to afford, after concomitant dehydration, the desired 3-benzylidene chromanones **5-10**. Indeed, aldol condensations of 2,2-disubstituted chroman-4-ones with benzaldehyde have been reported. For example, acid catalyzed aldol condensation of 2,2-diphenylchroman-4-one with benzaldehyde afforded 2,2-diphenyl-3-benzylidene-chroman-4-one after four days in 39% yield and base catalyzed aldol condensation of 6-cyano-2,2-dimethylchroman-4-one with benzaldehyde gave 6-cyano-2,2-dimethyl-3-benzylidene-chroman-4-one in 33% yield [2,3]. In our hands however, reaction of 6-methoxy-2,2-dimethylchroman-4-one **1** with various aldehydes under identical conditions provided only recovered starting materials. We reasoned that the cumulative effect of the electron donating effect of the 6-methoxy group coupled with the steric hindrance about the 2,2-dimethyl moiety was responsible for the reaction not proceeding. We next turned our attention to forming the silyl enol ether of **1** and reacting it in an aldol fashion. Silylation of chromanone **1** with trimethylsilylchloride, triethylamine and catalytic zinc chloride in refluxing tetrahydrofuran gave a 1:1 mixture of unreacted chromanone **1** and silyl enol ether **3** [4]. Reaction of the crude reaction mixture with benzaldehyde dimethyl acetal, commercially available as a 1:1 mixture of acetal and benzaldehyde, in the presence of zinc bromide gave aldol adduct **4** in a 7% yield overall (Scheme 1) [5]. Though the yield of **4** was low, we were encouraged that the reaction pathway was viable. Since we knew that the formation of silyl enol ether **3** was incomplete and that substituted benzaldehyde acetals are not commercially available in pure form, we set out to identify reaction conditions in which an *in situ* generated silyl enol ether would be immediately trapped by a substituted benzaldehyde.

Scheme 1



1 **3** **4**

A search of the literature uncovered the use of tetramethylorthosilicate in the presence of fluoride ion to affect Michael additions and aldol condensations [6,7]. The proposed mechanism (Figure 1) involves the formation of an *in situ* generated silyl enol ether *via* a fluoride ion activated pentacoordinate siliconium ion **I** [8]. The intermediate silyl enol ether is immediately trapped by the aldehyde **II** to give the aldol adduct **III**. Subsequent elimination affords the enone **IV** [9]. We therefore applied these conditions to our synthesis.

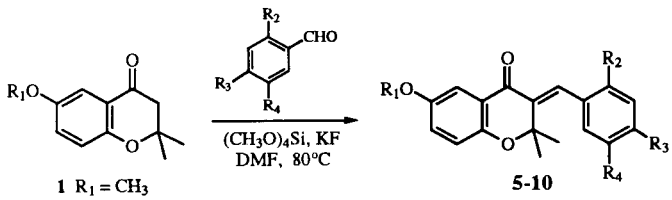


I **II** **III** **IV**

Figure 1

Thus, reaction of 6-methoxy-2,2-dimethylchroman-4-one **1** or 6-benzyloxy-2,2-dimethylchroman-4-one **2** with substituted benzaldehydes in the presence of tetramethylorthosilicate and potassium fluoride in dimethylformamide at 80° gave chromanones **5-10** (Scheme 2) in yields ranging from 34% to 73% (Table 1). Though the reaction conditions have not been optimized, the reaction times and yields appear to be dependent upon the substitution pattern of the benzaldehydes.

Scheme 2



1 $R_1 = CH_3$
2 $R_1 = PhCH_2$

5-10

Table 1

Entry	R_1	R_2	R_3	R_4	% Yield
5	CH_3	H	H	NO_2	60
6	$PhCH_2$	OCH_3	H	NO_2	67
7	CH_3	H	CO_2CH_3	H	73
8	CH_3	OCH_3	H	H	37
9	$PhCH_2$	OCH_3	H	CO_2CH_3	50
10	CH_3	H	Cl	H	34

The preparation of starting materials 6-methoxy-2,2-dimethylchroman-4-one **1** and 6-benzyloxy-2,2-dimethylchroman-4-one **2** are noteworthy in their own right. The preparation of chromanone **1** is well documented, however each method has limitations. For example, Fries rearrangement of 4-methoxyphenyl-3-methylbut-2-enonate under thermal or photochemical conditions as well as Friedel-Crafts acylation of 4-methoxyphenol with 3,3-dimethylacrylic acid proceed in low regioselectivity and yield [10,11]. Claisen rearrangement of γ-chloropropargyl-4-methoxyphenyl ether requires the problematic preparation of the dimethyl carbinyl ether [12]. Currently the most attractive route to chromanone **1** is the aldol condensation of 2-hydroxy-5-methoxyacetophenone with acetone followed by dehydration of the intermediate aldol adduct [13]. However we sought to apply the Kabbe condensation which accomplishes this transformation in one step to the synthesis of chromanones **1** or **2** [14]. Thus, reaction of 2-hydroxy-5-methoxyacetophenone or 2-hydroxy-5-benzyloxyacetophenone [15] with acetone in the presence of pyrrolidine with the azeotropic removal of water yielded chromanones **1** and **2** in a 53% and 47% yield respectively.

In conclusion, we have secured a general method for introducing a 3-benzylidene group in 6-alkoxy-2,2-dimethylchroman-4-ones **1** and **2** *via* an aldol condensation with substituted benzaldehydes in the presence of tetramethylorthosilicate and potassium fluoride. We believe this methodology has a much broader scope and the extension to other sterically or electronically encumbered bicyclic ketones might allow access to previously unobtainable aldol products.

EXPERIMENTAL

Melting points were determined using a Thomas-Hoover apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Bruker AC-300 spectrometer. Mass spectra were determined on a Hewlett-Packard 5989A mass spectrometer. Infrared spectra were acquired using either a Nicolet 510 FT spectrometer or a Perkin Elmer 283B spectrophotometer. Elemental analysis was performed by Schwarzkopf Microanalytical Laboratory, Woodside, NY.

Preparation of 6-Alkoxy-2,2-dimethyl-chroman-4-ones **1** and **2**.

General Procedure.

A mixture of 5-alkoxy-2-hydroxyacetophenone (1.0 equivalent), pyrrolidine (0.5 equivalent) and acetone (1.0 equivalent) in toluene (1 ml/0.1 g acetophenone) was stirred at room temperature for 3 hours, then refluxed over a Dean-Stark trap for 3 hours. An additional portion of pyrrolidine (0.5 equivalent) and acetone (1.0 equivalent) was added and the mixture refluxed over a Dean-Stark trap for 18 hours. The mixture was concentrated *in vacuo* and the residue dissolved in a minimal amount of methanol, poured into water, basified, then extracted with ethyl acetate. The organic extract was washed successively with water, brine, then dried (magnesium sulfate) and evaporated *in vacuo* to give crude product. Chromatography on silica gel eluting with ethyl acetate:hexanes solutions gave 6-alkoxy-2,2-dimethyl-chroman-4-ones **1** and **2**. Recrystallization from an appropriate solvent gave analytically pure compound.

6-Methoxy-2,2-dimethylchroman-4-one **1**.

This compound was obtained in a 53% yield as orange crystals (ether:hexanes) mp 71-73°; ^{1}H-nmr (deuteriochloroform): δ 7.29 (d, J = 3 Hz, 1H), 7.08 (dd, J = 3, 9 Hz, 1H), 6.85 (d, J = 9 Hz, 1H), 3.79 (s, 3H), 2.70 (s, 2H), 1.44 (s, 6H); ms: (chemical ionization) m/z 224 (M^+ + 18, 24), 207 (M^+ + 1, 100); ir (potassium bromide): 1678 (CO) cm^{-1}.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.85; H, 7.08.

6-Benzyloxy-2,2-dimethylchroman-4-one **2**.

This compound was obtained in 47% yield as yellow crystals (ethyl acetate:hexanes) mp 105-107°; ^{1}H-nmr (deuteriochloroform): δ 7.39 (m, 6H), 7.16 (dd, J = 3, 9 Hz, 1H), 6.88 (d, J = 9 Hz, 1H), 5.04 (s, 2H), 2.70 (s, 2H), 1.45 (s, 6H); ms: (chemical ionization) m/z 300 (M^+ + 18, 100); ir (potassium bromide): 1690 (CO) cm^{-1} .

Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.16; H, 6.42.

Preparation of 6-Alkoxy-2,2-dimethyl-3-benzylidenechroman-4-ones **5-10**.

General Procedure.

A mixture of chromanes **1** or **2** (1.0 equivalent), tetramethylorthosilicate (1.1 equivalents), potassium fluoride (1.1 equivalents) and aldehyde (1.1 equivalents) in dry dimethylformamide (5 ml/g chromanone **1** or **2**) was heated at 80° until the reaction was judged complete by thin layer chromatography. The reaction mixture was diluted with ethyl acetate and washed successively with 1 *N* hydrochloric acid, 1 *N* potassium hydroxide, water, brine, then dried (magnesium sulfate) and concentrated *in vacuo* to give crude product. Chromatography on silica gel eluting with ethyl acetate:hexanes solutions gave 6-alkoxy-2,2-dimethyl-3-benzylidenechroman-4-ones **5-10**. Recrystallization from an appropriate solvent gave an analytically pure compound.

6-Methoxy-2,2-dimethyl-3-(3-nitrobenzylidene)chroman-4-one **5**.

This compound was obtained in a 60% yield as yellow crystals (ether:hexanes) mp 103-105°; ^{1}H-nmr (deuteriochloroform): δ 8.29 (s, 1H), 8.16 (d, J = 8 Hz, 1H), 7.75 (d, J = 8 Hz, 1H), 7.50 (t, J = 8 Hz, 1H), 7.26 (s, 1H), 7.11 (dd, J = 3, 9 Hz, 1H), 6.97 (s, 1H), 6.88 (d, J = 9 Hz, 1H), 3.78 (s, 3H), 1.70 (s, 6H); ms: (chemical ionization) m/z 357 (M^+ + 18, 50), 340 (M^+ + 1, 100); ir (potassium bromide): 1680 (CO) cm^{-1}.

Anal. Calcd. for $C_{19}H_{17}NO_5$: C, 67.25; H, 5.05; N, 4.13. Found: C, 67.22; H, 4.87; N, 4.11.

6-Benzyloxy-3-(2-methoxy-5-nitrobenzylidene)-2,2-dimethylchroman-4-one **6**.

This compound was obtained in a 67% yield as yellow crystals (ethyl acetate:hexanes) mp 110-112°; ^{1}H-nmr (deuteriochloroform): δ 8.31 (d, J = 3 Hz, 1H), 8.21 (dd, J = 3, 9 Hz, 1H), 7.40 (m, 6H), 7.18 (dd, J = 3, 9 Hz, 1H), 6.90 (t, J = 7 Hz, 3H), 5.02 (s, 2H), 3.82 (s, 3H), 1.69 (s, 6H); ms: (chemical ionization) m/z 463 (M^+ + 18, 95), 446 (M^+ + 1, 100); ir (potassium bromide): 1675 (CO) cm^{-1}.

Anal. Calcd. for $C_{26}H_{23}NO_6$: C, 70.10; H, 5.20; N, 3.14. Found: C, 70.05; H, 5.35; N, 2.79.

4-(6-Methoxy-2,2-dimethyl-4-oxochroman-3-ylidenemethyl)-benzoic Acid Methyl Ester **7**.

This compound was obtained in a 73% yield as orange crystals (ethyl acetate:hexanes) mp 179-181°; ^{1}H-nmr (deuteriochloroform): δ 8.00 (d, J = 8 Hz, 2H), 7.46 (d, J = 8 Hz, 2H), 7.29 (d, J = 3 Hz, 1H), 7.10 (dd, J = 3, 9 Hz, 1H), 6.97 (s, 1H), 6.87 (d, J = 9 Hz, 1H), 3.91 (s, 3H), 3.79 (s, 3H), 1.68 (s, 6H); ms: (chemical ionization) m/z 353 (M^+ + 1, 100); ir (potassium bromide): 1722, 1711, 1665 (CO) cm^{-1}.

Anal. Calcd. for $C_{21}H_{20}O_5$: C, 71.58; H, 5.72. Found: C, 71.15; H, 5.98.

6-Methoxy-3-(2-methoxybenzylidene)-2,2-dimethylchroman-4-one **8**.

This compound was obtained in a 37% yield as an oil; ^{1}H-nmr (deuteriochloroform): δ 7.40 (dd, J = 1, 7 Hz, 1H), 7.33 (d, J = 3 Hz, 1H), 7.28 (d, J = 9 Hz, 1H), 7.07 (m, 2H), 6.87 (m, 3H), 3.78 (s, 3H), 1.68 (s, 6H); ms: (chemical ionization) m/z 325 (M^+ + 1, 100); ir (chloroform): 1720 (CO) cm^{-1}.

Anal. Calcd. for $C_{20}H_{20}O_4$: C, 74.06; H, 6.21. Found: C, 73.67; H, 6.42.

3-(6-Benzyloxy-2,2-dimethyl-4-oxo-chroman-3-ylidenemethyl)-4-methoxybenzoicAacid Methyl Ester **9**

This compound was obtained in a 50% yield as yellow crystals (ethyl acetate:hexanes) mp 145-147°; ^{1}H-nmr (deuteriochloroform): 8.07 (d, J = 2 Hz, 1H), 8.00 (dd, J = 2, 9 Hz, 1H), 7.40 (m, 6H), 7.16 (dd, J = 3, 9 Hz, 1H), 6.91 (m, 3H), 5.02 (s, 2H), 3.88 (s, 3H), 3.76 (s, 3H), 1.69 (s, 6H); ms: (chemical ionization) m/z 476 (M^+ + 18, 80), 459 (M^+ + 1, 100); ir (potassium bromide): 1720, 1680 (CO) cm^{-1}.

Anal. Calcd. for $C_{28}H_{26}O_6$: C, 73.35; H, 5.72. Found: C, 73.47; H, 5.89.

3-(4-Chlorobenzylidene)-6-methoxy-2,2-dimethylchroman-4-one **10**.

This compound was obtained in a 34% yield as yellow crystals (ethyl acetate:hexanes) mp 143-145°; ^{1}H-nmr (deuteriochloroform): δ 7.40 (d, J = 8 Hz, 2H), 7.29 (m, 3H), 7.09 (dd, J = 3, 9 Hz, 1H), 6.87 (m, 2H), 3.79 (s, 3H), 1.67 (s, 6H); ms: (chemical ionization) m/z 330 (M^+ + 1, 100); ir (potassium bromide): 1664 (CO) cm^{-1}.

Anal. Calcd. for $C_{19}H_{17}O_3Cl$: C, 69.41; H, 5.21. Found: C, 69.34; H, 5.11.

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