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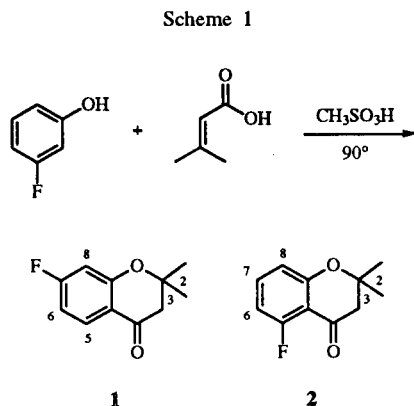
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Reaction of 3-fluorophenol and 3,3-dimethylacrylic acid in methanesulfonic acid at 90° gives predominantly 5-fluoro-2,2-dimethylchroman-4-one, not the 7-fluoro isomer as reported [1].

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We recently required a quantity of 7-fluoro-2,2-dimethylchroman-4-one (**1**). Two routes to this compound have been reported. A one step procedure to **1** [1] involves cyclization of 3-fluorophenol and 3,3-dimethylacrylic acid in methanesulfonic acid (Scheme 1). An alternate method for preparation of **1** [2,3] also starts with 3-fluorophenol, and proceeds *via* intermediates **3** and **4** (Scheme 2). We initially examined the route shown in Scheme 1. Repetition of this procedure as described, however, affords instead a mixture of two isomeric compounds. The major product formed is 5-fluoro-2,2-dimethylchroman-4-one (**2**); only a trace amount of **1** is in fact produced under these conditions.

In 1990, a report appeared [1] claiming the synthesis of 7-fluoro-2,2-dimethylchroman-4-one (**1**), *via* 3-fluorophenol and 3,3-dimethylacrylic acid, as shown in Scheme 1.

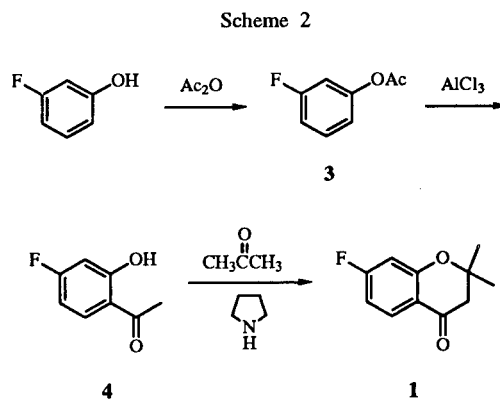


The product, **1**, was reportedly obtained in 29% yield after chromatography. Mass spectral analysis of **1** showed a parent ion at *m/e* 194, as well as the base peak at *m/e* = 179 corresponding to the loss of one methyl group. No other spectral or analytical characterization for **1** was provided.

We repeated this reaction under identical conditions to those reported. The <sup>1</sup>H nmr analysis of the crude product obtained revealed what was subsequently shown to be a *ca.* 1:10 mixture of **1** and **2**. Chromatography in 7:1 petroleum ether-ethyl acetate (the published column eluent) afforded a 47% yield of a product homogeneous on tlc in this eluent. However, the nmr spectrum of this product

revealed the same 1:10 mixture of **1** and **2** as seen in the crude material. Further tlc analysis using multiple elution in a ternary system of pentane, methylene chloride, and diethyl ether clearly showed that two compounds were present. Flash chromatography in this eluent cleanly separated pure **2** (21% yield) as the faster moving spot. In addition, a 7% yield of material was isolated which was still a *ca.* 1:1 mixture of **1** and **2**.

In order to secure an authentic sample of pure **1** for comparison, we then repeated the synthetic method for the synthesis of **1** shown in Scheme 2.



The requisite intermediate 4'-fluoro-2'-hydroxyacetophenone (**4**) was prepared as reported [3]. 3-Fluorophenol was acetylated to provide 3-fluorophenyl acetate (**3**). Fries rearrangement of **3** was carried out in aluminum chloride at 160°. The <sup>1</sup>H nmr spectrum of **4** (see Experimental) confirmed the assigned structure, as in particular the doublet of doublets present at δ 7.70 (*J* = 5, 9 Hz) could be conclusively assigned to H<sub>6</sub> (*J*<sub>5,6</sub> = 9; *J*<sub>6,F</sub> = 5) [4].

The intermediate acetophenone **4** was then converted to **1** under conditions similar to those reported (acetone, pyrrolidine, methanol) [2]. The nmr absorbances for the sample of pure **1** obtained in this fashion correspond exactly with the peaks from the minor component of the reaction product from Scheme 1.

A side-by-side comparison of the nmr data for **1** and **2** leave no doubt that these structural assignments are

Table 1

	H <sub>5</sub>	H <sub>6</sub>	H <sub>7</sub>	H <sub>8</sub>	J <sub>5,6</sub>	J <sub>6,7</sub>	J <sub>6,8</sub>	J <sub>7,8</sub>	J <sub>5,F</sub>	J <sub>6,F</sub>	J <sub>7,F</sub>	J <sub>8,F</sub>
1	7.88	6.69	—	6.62	8.6	—	2.4	—	6.7	8.6	—	10.0
2	—	6.85	7.26	6.79	—	8.4	2.6	9.0	—	8.4	[a]	0.0

[a] This coupling constant could not be determined.

correct (Table 1).

All of the chemical shift data observed for **1** and **2** are in close agreement with calculated values [5]. In particular, the absorbance at  $\delta$  7.88 can only be assigned to H<sub>5</sub> of **1**. The magnitude of the H-F coupling constants observed is also within the ranges reported [6].

The mass spectral data obtained for our samples of **1** and **2** as well as those reported for **1** [1] are presented below in Table 2.

Table 2

	M <sup>+</sup>	Other Peaks (%)
1	194 (39)	179 (100), 139 (82), 138 (45), 110 (41)
2	194 (67)	179 (100), 152 (18), 151 (20), 137 (23), 123 (17), 109 (28)
1 (reported [1])	194 (25)	179 (100), 152 (14), 109 (27)

The fragmentation patterns observed for our samples of **1** and **2** are similar, as both give a prominent parent ion, and a base peak corresponding to loss of one methyl group. Subsequent fragmentation is also similar, however **1** does not show a peak at  $m/e = 152$ , whereas **2** does. The data reported for **1** [1] more closely correspond to those we obtained for **2**, further substantiating the structural assignments.

The effect of modifying the temperature of the methanesulfonic acid reaction to form **1** and **2** was briefly studied to see whether the isomer ratio could be influenced. Although the reaction proceeded more slowly at lower temperatures, by tlc the ratio of **1** to **2** appeared similar when the reaction was carried out at either 25° or 60°.

The cyclization which we have observed to give predominantly **2** does not appear to follow precedent for similar cyclizations. For example, 4-(3-fluorophenyl)butyric acid in polyphosphoric acid gives a 70% yield of 6-fluorotetralone; no mention of formation of 8-fluorotetralone (cyclization *ortho* to the fluorine) is made [7].

## EXPERIMENTAL

Melting points were determined on a Gallenkamp apparatus, and are uncorrected. Infrared spectra were measured on a Perkin-Elmer 137. Proton nuclear magnetic resonance spectra were recorded at 100 MHz on a Bruker WP 100SY, or at 400

MHz on a Varian XL400. Coupling constants are measured in hertz. Elemental analyses were performed by Atlantic Microlab. Thin-layer chromatography was carried out on Baker Si 250F plates. Visualization was accomplished with ultraviolet exposure or treatment with phosphomolybdic acid. Flash chromatography was carried out on Baker silica gel (40  $\mu$ M).

7-Fluoro-2,2-dimethylchroman-4-one (**1**) and 5-Fluoro-2,2-dimethylchroman-4-one (**2**).

A mixture of 71.0 g (0.709 mole) of 3,3-dimethylacrylic acid and 20.0 g (0.178 mole) of 3-fluorophenol in 400 ml of methanesulfonic acid was heated at 90-95° for 20 hours. After being cooled to 25°, the reaction mixture was poured into 600 ml of ice and 600 ml of water. The aqueous layer was extracted with 3 x 350 ml of ether. The combined organic phase was washed with 3 x 150 ml of water, 4 x 180 ml of cold 1 *N* sodium hydroxide, 2 x 200 ml of water, and 1 x 250 ml of saturated sodium chloride solution. The ether layer was dried (magnesium sulfate) and evaporated. The oil that resulted was pumped on at high vacuum for 2 days with stirring to afford 48.63 g of a red-brown oil. The <sup>1</sup>H nmr analysis of this material showed a prominent singlet at  $\delta = 2.61$  ppm (H<sub>3</sub> of **2**) as well as a much smaller singlet at  $\delta = 2.69$  ppm (H<sub>3</sub> of **1**); the ratio was about 10:1. A major spot at  $R_f = 0.32$  (7:1 petroleum ether:ethyl acetate) was evident. A 4.0 g sample of the crude product was purified by flash chromatography on 120 g of silica gel, elution with 7:1 petroleum ether:ethyl acetate. Pure fractions were combined to afford 1.35 g (47%) of a *ca.* 1:10 mixture (by nmr) of **1** and **2**.

This material was repurified by flash chromatography on 140 g of silica gel, elution with 3% methylene chloride and 3% ether in pentane, followed by 4% methylene chloride and 4% ether in pentane. Pure **2** eluted first, and the combined fractions gave 0.587 g of **2** as a pink solid, mp 47-49° (21%). Later fractions gave 0.162 g (6%) of a solid which was about 93% pure **2** by nmr. Subsequent fractions afforded 0.207 g (7%) of a yellow oil which by nmr was about 55% **2** and 45% **1**.

Pure **2** had  $\nu$  (potassium bromide): 1755  $\text{cm}^{-1}$  [9]; <sup>1</sup>H nmr (400 MHz, deuteriochloroform):  $\delta$  7.24-7.28 (m, 1H), 6.85 (dt, 1H,  $J = 2.6, 8.4$ ), 6.79 (dd, 1H,  $J = 2.6, 9.0$ ), 2.62 (s, 2H), 1.34 (s, 6H); ms (electron impact, 70 electron volts):  $m/z$  194 (67), 179 (M<sup>+</sup>-CH<sub>3</sub>, 100).

*Anal.* Calcd. for C<sub>11</sub>H<sub>11</sub>FO<sub>2</sub>: C, 68.03; H, 5.71. Found: C, 68.21; H, 5.76.

The combined later fractions which were comprised of roughly equal amounts of **1** and **2** displayed the following <sup>1</sup>H nmr spectrum (100 MHz, deuteriochloroform):  $\delta$  7.81-8.00 (m, 1H, C<sub>5</sub>-H of **1**), 7.1-7.3 (m, 1H, C<sub>7</sub>-H of **2**), 6.5-7.0 (m, 4H, C<sub>6</sub>-H and C<sub>8</sub>-H of **1** and **2**), 2.70 (s, 2H, CH<sub>2</sub> of **1**), 2.63 (s, 2H, CH<sub>2</sub> of **2**), 1.46 (s, 6H, CH<sub>3</sub> of **1**), 1.35 (s, 6H, CH<sub>3</sub> of **2**). Thin-layer chromatography (88% pentane, 6% ether, 6% methylene chloride, three elutions) gave: for **1**  $R_f = 0.37$ ; for **2**  $R_f = 0.43$ .

3-Fluorophenyl Acetate (**3**).

The published procedure [3] was followed to afford **3** in 92% yield as a clear oil;  $^1\text{H}$  nmr (100 MHz, deuteriochloroform):  $\delta$  7.1-7.5 (m, 1H,  $\text{C}_5\text{-H}$ ), 6.7-7.0 (m, 3H,  $\text{C}_{2,4,6}\text{-H}$ ); 2.30 (s, 3H,  $\text{CH}_3$ ).

4'-Fluoro-2'-hydroxyacetophenone (**4**).

The published procedure [3] was followed to give **4** in 93% yield as an oil (lit [3] mp 24°);  $^1\text{H}$  nmr (100 MHz, deuteriochloroform):  $\delta$  12.5 (apparent doublet, 1H,  $\text{OH}$ ), 7.70 (dd, 1H,  $\text{J} = 5, 9$ ,  $\text{C}_6\text{-H}$ ), 6.5-6.8 (m, 2H,  $\text{C}_{3,5}\text{-H}$ ); 2.62 (s, 3H,  $\text{CH}_3$ ).

7-Fluoro-2,2-dimethylchroman-4-one (**1**).

The procedure for the conversion of 5'-fluoro-2'-hydroxyacetophenone to 6-fluoro-2,2-dimethylchroman-4-one [8] was followed. A solution of **4** (6.55 g, 0.0425 mole), acetone (3.80 g, 0.0654 mole), and pyrrolidine (4.6 g, 0.0647 mole) in 165 ml of methanol was stirred at 25° overnight. The next day the reaction mixture was concentrated to an orange oil. One fourth of this oil was purified by flash chromatography on silica gel (elution with 25% methylene chloride/hexanes). Pure fractions were combined and concentrated to afford 1.18 g (57%) of **1** as a white solid, mp 45-46° (lit [2] oil); ir (potassium bromide): 1675  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (400 MHz, deuteriochloroform):  $\delta$  7.88 (dd, 1H,  $\text{J} = 6.7, 8.6$ ), 6.69 (dt, 1H,  $\text{J} = 2.4, 8.6$ ), 6.62 (dd, 1H,  $\text{J} = 2.4, 10.0$ ), 2.71 (s, 2H), 1.46 (s, 6H); ms: (electron impact, 70 electron volts)  $m/z$  194 (39), 179 ( $\text{M}^+ - \text{CH}_3$ , 100).

*Anal.* Calcd. for  $\text{C}_{11}\text{H}_{11}\text{FO}_2$ : C, 68.03; H, 5.71. Found: C, 67.90; H, 5.79.

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#### REFERENCES AND NOTES

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- [2] C. A. Lipinski, European Patent Application EP 230,379 (1987); *Chem. Abstr.*, **108**, 75224h (1988).
- [3] R. Henning, R. Lattrell, H. J. Gerhards, and M. Leven, *J. Med. Chem.*, **30**, 814 (1987).
- [4] The isomeric 2'-fluoro-6'-hydroxyacetophenone (which would lead to **2**) could not have been formed in place of **4**, since in 2'-fluoro-6'-hydroxyacetophenone the furthest downfield proton would be *para* to the carbonyl and would be coupled to two *ortho* protons as well as to a *meta*-oriented fluorine.
- [5] L. M. Jackman and S. Sternhell, Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry, 2nd edition, Pergamon Press, Oxford, 1969, p 202.
- [6] Reference 5, p 349.
- [7] W. M. Owton and M. Brunaus, *Synth. Commun.*, **21**, 981 (1991).
- [8] S. P. Brown, A. L. Cooper, J. L. Longridge, J. J. Morris, and J. Preston, British Patent GB 2,227,744 (1990); *Chem. Abstr.*, **114**, 142290r (1991).
- [9] The very low frequency for the carbonyl of **5** can be explained by the close proximity of the adjacent fluorine atom (see L. J. Bellamy, The Infrared Spectra of Complex Molecules, 2nd edition, Chapman and Hall, New York, 1980, p 154 for a similar example).