# The Synthesis of 2-Methylchromone-3-carboxylic Acid



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A new synthesis of 2-methyl-4-oxo-4*H*-1-benzopyran-3-carboxylic acid (2-methylchromone-3-carboxylic acid from salicyloyl chloride and the enamine of ethyl acetoacetate, is described and compared with the classical synthesis.

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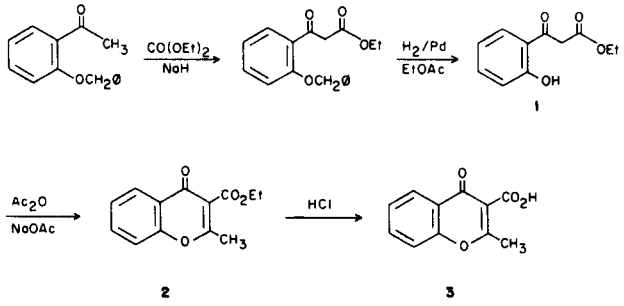
In connection with other synthetic work, we have attempted to synthesize 2-methyl-4-oxo-4*H*-1-benzopyran-3-carboxylic acid (2-methylchromone-3-carboxylic acid) **3** using the method of Klutchko (1). Beginning with *o*-benzyloxyacetophenone we succeeded in obtaining a very low yield of the chromone acid as outlined below.

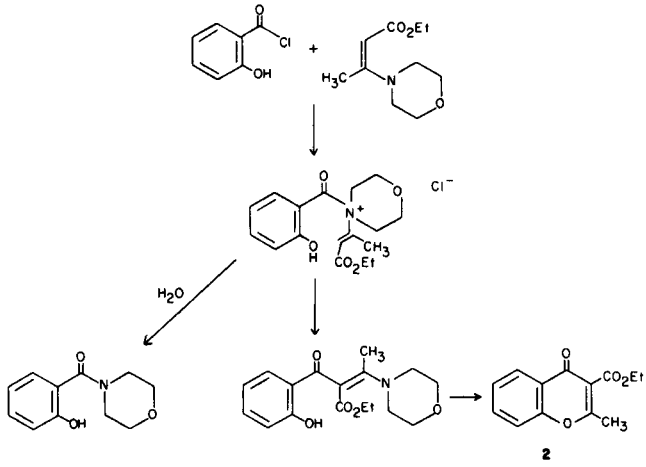



**2** **3**

The conversion of **1** to **2** proved to be a major obstacle in this synthesis and although Klutchko reported a 62% yield for the analogous methyl ester (1), we were unable to obtain yields above 35% for this step. Due to the low yield and rather tedious procedure, we sought a more direct route to the chromone-3-carboxylic acid.

It was reasoned that the direct condensation of salicyloyl chloride with ethyl acetoacetate might be more straightforward. An enamine condensation was chosen as other basic catalysts can cause polymerization of the acid chloride and/or rearrangement of the chromone to an hydroxy coumarin (1). The method also has the advantage that remaining amino and phenolic or enolic by-products can be removed by extraction with acid and base, respectively.

Thus, to an ice cold solution of the salicyloyl chloride in methylene chloride was added two equivalents of ethyl acetoacetate morpholine enamine. Immediate work-up gave a quantitative yield of morpholine salicylamide, which presumably derives from an initial rapid acylation of the enamine nitrogen. If the reaction mixture is stirred for three days at 25°and then worked up with acid and base wash, a 36% yield of the crude chromone ethyl ester **2** is obtained as a deep red oil which crystallizes on standing. Treatment of the crude ester with concentrated hydrochloric acid at 100° yields the chromone acid **3** as pale




**2**

buff crystals, which are essentially free of all impurities.

Although the overall yield of 17%, based on the salicyloyl chloride, is low, the simplicity of the method, the purity of the product and the cost of starting materials make this synthesis superior to that reported by Klutchko (1).

## EXPERIMENTAL

Nmr, ir and mass spectra were obtained using a Varian EM360, a Unicam SP1000 and a Finnegan 1015 spectrometer respectively. Melting points are uncorrected.

*O*-Benzyloxyacetophenone.

The compound was prepared from *o*-hydroxyacetophenone, 136 g. and benzyl chloride, 150 g. to give 192 g. (85%) after distillation, using the method of Pandit and Bruce (2).

Ethyl (2-Benzyloxybenzoyl)acetate.

The procedure of Okumura, *et al.* (3) was modified to advantage. A mixture of ethyl carbonate (250 ml., 2.12 moles) and sodium hydride (20 g. 50% oil dispersion) was heated to 80° under nitrogen. *O*-Benzyloxyacetophenone (49.7 g., 0.22 mole) was added with stirring over 20 minutes. The mixture was cooled, diluted with dry ether, filtered and evaporated *in vacuo* (4). The crude product was filtered through silica gel (eluant, chloroform) to give 34.6 g. (61%) of product which is essentially free of impurities (nmr assay) (3).

Ethyl (2-Hydroxybenzoyl)acetate, (Ethyl Salicyloylacetate).

The hydrogenolysis was carried out according to the procedure of Okumura (3) using ethyl acetate as a solvent. The use of ethyl

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alcohol led to carbonyl reduction. Thus, ethyl (2-benzyloxybenzoyl)acetate (5 g., 0.167 mole) was hydrogenated over palladium/carbon (400 mg., 5%) to give 3.6 g. (96%) of the phenol.

Ethyl 2-Methyl-4-oxo-4*H*-1-benzopyran-3-carboxylate, (Ethyl 2-Methylchromone-3-carboxylate). A.

The procedure of Klutcho (1) was tried and modified with little success. The most successful attempt is reported. Ethyl salicyloylacetate (6 g., 0.029 mole), acetic anhydride (40 ml.) and sodium acetate (2.5 g. anhydrous) were heated to 105° with stirring for 3 hours. The solution was cooled, diluted with benzene, filtered and the filtrate stirred for 2 hours with water (100 ml.). The organic layer was dried (magnesium sulfate) and evaporated to give 3 g. of crude product. Chromatography on silica gel (eluant benzene/ether 9:1) gave 1.9 g. (32%) of the pure ester (see method B below for properties).

Ethyl 2-Methyl-4-oxo-4*H*-1-benzopyran-3-carboxylate, (Ethyl 2-Methylchromone-3-carboxylate). B.

Salicyloyl chloride (164 g., 1.05 moles) in dry methylene chloride (400 ml.) was added dropwise to a cooled (0°-5°) solution of ethyl 3-morpholino-2-butene carboxylate (200 g., 2.2 moles) in 1 liter of methylene chloride over a period of one hour with stirring. The mixture was stirred at room temperature for 70 hours, then refluxed for 3 hours. The cooled solution was washed successively with 1 liter each, of 1.5 *N* hydrochloric acid (4 times) then 2.5 *N* potassium hydroxide (4 times). The organic phase was dried (magnesium sulfate) and evaporated *in vacuo* yielding 84 g. (36%) of a deep red oil which crystallized on standing. A sample was purified by sublimation under high vacuum giving white crystals, m.p. 63-65°; ir (nujol): 1635 (pyrone C=O), 1730 $cm^{-1}$ (ester C=O); nmr (deuteriochloroform): $\delta$ 8.15 (q, 1, H-5), 7.17-7.80 (m, 3, H-6,7,8), 4.42 (q, 2, $-CO_2CH_2CH_3$), 2.50 (s, 3, $CH_3$), 1.42 (t, 3, $-CO_2CH_2CH_3$): ms: m/e (relative intensity) 232 (7), 202 (16), 187 (71), 160 (100), 121 (89), 120 (71).

*Anal.* Calcd. for $C_{13}H_{12}O_4$: C, 67.24; H, 5.21. Found: C, 67.45; H, 5.29.

2-Methyl-4-oxo-4*H*-1-benzopyran-3-carboxylic Acid, (2-Methylchromone-3-carboxylic Acid).

The crude ethyl 2-methyl-4-oxo-4*H*-1-benzopyran-3-carboxylate (84 g.) was taken up in hydrochloric acid (500 ml., 12 *N*) and heated on a boiling water bath under a reflux condenser for 1.5 hours. This was poured onto ice (500 g.), extracted into chloroform and from the chloroform into saturated aqueous sodium bicarbonate. Acidification of the bicarbonate solution and filtration gave 35 g. (47%) of pale buff crystals. Recrystallization from 2-propanol gave pale yellow crystals with spectral data (ir, nmr, ms) identical to those reported by Kluchko (1).

Acknowledgment.

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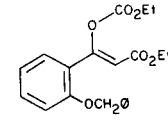
## REFERENCES AND NOTES

(1) S. Klutchko, J. Shavel Jr. and M. von Strandtman, *J. Org. Chem.*, **39**, 2436 (1974).

(2) U. K. Pandit and T. C. Bruce, *J. Am. Chem. Soc.*, **82**, 3386 (1960).

(3) K. Okumura, K. Kondo, T. Oine and I. Inoue, *Chem. Pharm. Bull.*, **22**, 331 (1974).

(4) The product of this reaction is probably




which hydrolyses when filtered through silica gel. Hydrolysis with dilute aqueous acid gave a less pure product.