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A Practical Preparation of 7-Methoxy-3(2H)-benzofuranone

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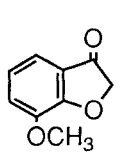
Abstract: A practical new synthesis suitable for large-scale production of 7-methoxy-3(2H)-benzofuranone by conversion of commercially available 2-hydroxy-3-methoxybenzoic acid to 7-methoxy-3-acetoxybenzofuran followed by hydrolysis is described.

Substituted 3(2H)-Benzofuranones are useful intermediates for preparing benzofurans functionally substituted at the 3-position[1] and other heterocycles such as 3-(3-benzofuranyl)coumarins[2] and benzofuro[3,2-b]indoles.[3] In particular, 7-methoxy-3(2H)-benzofuranone (**1**) is a key intermediate in Ciganek's synthesis of 2,3,4,4a,5,6,7,7a-octahydro-1H-benzofuro[3,2-e]isoquinoline (**2**),[4] a morphine (**3**) fragment which contains the complete skeleton of morphine except for ring B and C-10. However, the syntheses described in the literature[1,5] for **1** are not amenable to large-scale operation for reasons such as unreliable yields and purity, tedious extractions and evaporations, and the use of diazomethane.



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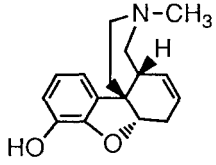

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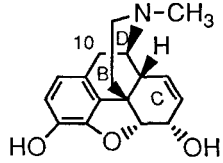

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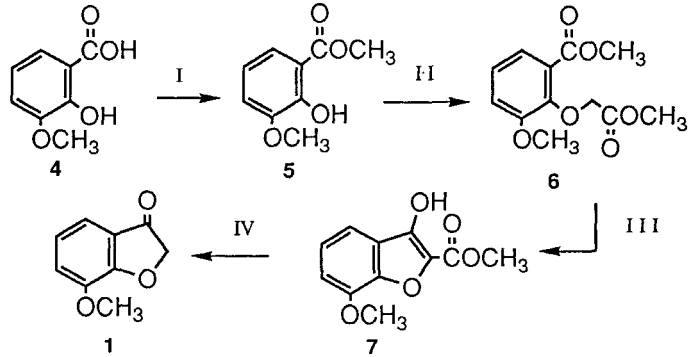
We have developed a new synthesis which has none of these complications, and allows for the production of multi-gram or kilogram quantities of **1**. The process requires only simple reagents and reaction conditions, and starts from commercially available 2-hydroxy-3-methoxybenzoic acid. All of the intermediates crystallize in good yields from their respective reaction mixtures upon work-up, and are used in subsequent steps without further purifications or recrystallizations. The key steps are the formation of the enol acetate, 7-methoxy-3-acetoxybenzofuran, via an intramolecular Perkin condensation, followed by a facile acid hydrolysis to form **1**. The overall yield of **1** from the 5-step process is 50-55%.

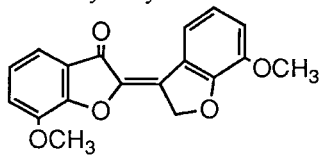
The original synthesis we used for preparing **1**, illustrated in Scheme 1, was based upon improving analogous chemistry described by Schroeder et.al. for preparing unsubstituted and halogen substituted benzofuranones.[3]



Scheme 1: I: Methanol, H_2SO_4, 68 °C; II: $ClCH_2CO_2CH_3$, K_2CO_3, Acetone, 57 °C; III: (1) $NaOCH_3$, Methanol, 65 °C, (2) HCl, Water; IV: Phosphoric acid, Acetic acid, Water, 100 °C

Modifications we made to the original chemistry improved the overall yield and feasibility by shortening reaction times and improving isolation procedures. However, the crude final product crystallized slowly, was highly colored, and had a low melting-point. We also had problems reproducing the batch-to-batch purity of the ß-keto ester **7**, and the Step IV hydrolysis was quite problematic. We examined a variety of acidic hydrolysis schemes until we settled on an aqueous acetic acid/phosphoric acid mixture at ~100 °C as the preferred system. Nevertheless, ^1H NMR monitoring of Step IV showed that significant product degradation occurred

after the reaction had proceeded beyond 50% conversion, suggesting dimerization via aldol condensation followed by dehydration to form **8**.



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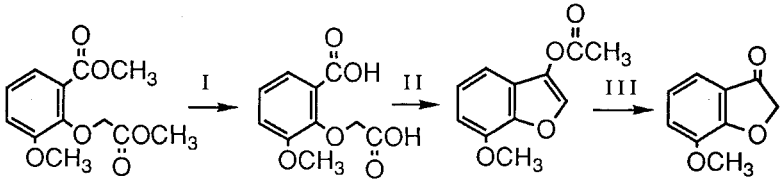
Jung and Abrecht[5] also expressed dissatisfaction with this route, and elaborated on an alternative 3-step synthesis, first described by Richtzehain and Alfredsson[6] and further studied by Dallacker and Forb.[7] Their route involves converting 2,3-dimethyoxybenzoic acid to the acid chloride, treating with ethereal diazomethane and then acetic acid to obtain **1** in 64% yield. While this short laboratory synthesis may be convenient for preparing several grams, it would not be amenable to larger scale operations, in particular, due to the hazards associated with diazomethane.

Our new alternative synthetic route is illustrated in Scheme 2.



6 **9** **10** **1**

Scheme 2: I: NaOH, Water, Methanol, 82 °C; II: Sodium acetate, Acetic acid, Acetic anhydride, 125 °C; III: HCl, Water, Methanol, 68 °C.

Previous work by Carvalho and Sargent[8] had demonstrated that 2-(carboxy-methoxy)benzoic acid could be converted to 3-acetoxybenzofuran via an intramolecular Perkin[9] condensation. Acid hydrolysis of this intermediate gave 3(2H)-benzofuranone in 38% overall yield from the diacid.

Since we already had a good synthesis of the diester **6,** we hydrolyzed it to prepare the diacid **9** in 90-95 % yield. We were then fortunate to find that **10** crystallized readily from the reaction mixture simply by adding water (unlike 3-acetoxy-benzofuran which Carvalho and Sargent extracted and obtained as an oil). In the final hydrolysis step, we optimized the hydrochloric acid concentration in order to

reduce by-product formation. Thus, we were able prepare very pure **1** in 65% yield from the diacid.

Experimental: All starting materials were of reagent grade, and were used as obtained from the distributor. 2-Hydroxy-3-methoxybenzoic acid and methyl chloroacetate were purchased from Aldrich Chemical Co, Inc. Melting points were measured using a Mettler-Toledo TA800 Differential Scanning Calorimeter. ^{1}H NMR spectra were obtained using a Varian Unity 300 NMR spectrometer. Chemical shifts are provided as δ values relative to $(CH_3)_4Si$. Mass spectra were obtained using a Perkin-Elmer/SCIEX API III triple quadrupole mass spectrometer using positive or negative pneumatically assisted electrospray (ES). Samples were ionized in 50:50 acetonitrile:water containing 0.1% formic acid. Elemental analyses were performed by Quantitative Technologies, Inc., Whitehouse, New Jersey.

2-Hydroxy-3-methoxybenzoic acid, methyl ester (**5**): An agitated mixture of methanol (700 mL), concentrated sulfuric acid (33 mL), and 2-hydroxy-3-methoxybenzoic acid (200.0 g, 1.19 M) was heated at reflux for 24 hours. After cooling to 25 °C to crystallize the product, water (1.2 L) was added slowly to fully precipitate the product. The mass was then cooled to 10-15 °C for 2 hours, and the product was collected by filtration, washed with water, and dried under vacuum at 45-50 °C to obtain 202.3 g (94%) of fine slightly-pink crystals. Melting point: 68.1 °C (Lit [10] mp: 67 °C). ^{1}H NMR (DMSO-d_6) δ 3.8 (s, 3H), 3.9 (s, 3H), 6.9 (t, 1H), 7.2 (d, 1H), 7.35 (d, 1H), 10.5 (s, 1H).

3-Methoxy-2-(2-methoxy-2-oxoethoxy)benzoic acid, methyl ester (**6**): Anhydrous potassium carbonate (362 g) was added to an agitated solution of **5** (190.0 g, 1.04 M) in dry acetone (1900 mL). Methyl chloroacetate (182 mL) was then added dropwise, and the mixture was heated to reflux for 48 hours. After cooling to room temperature, the slurry was filtered through a bed of filter aid, the filter cake washed with fresh acetone (200 mL), and the combined wash and filtrate concentrated by distillation to approximately 800 mL. After cooling, water (2.2 L) was then added over 1.5 hours to precipitate the product. After stirring overnight, the product was collected by filtration, washed with water, and dried under vacuum at 45 °C to obtain 222.2 g (84%) of coarse white crystals. Melting point: 75.5 °C.

(Lit[11] mp: 73-74 °C) ^{1}H NMR (DMSO-d_6) δ 3.7 (s, 3H), 3.8 (s, 3H), 3.83 (s, 3H), 4.6 (s, 2H), 7.25 (m, 3H).

2-(Carboxymethoxy)-3-methoxybenzoic acid (**9**): A mixture of **6** (235.0 g, 0.96 M) and methanol (460 mL) was heated to 60 °C. Aqueous 12% sodium hydroxide (1150 g) was added over 30 minutes such that the temperature remained below 72 °C during the addition. After heating at reflux (82 °C) for 60 minutes, the mixture was cooled to room temperature, and acidified to pH 2 with aqueous 22% hydrochloric acid (500 mL). The product wascollected by filtration, washed with water (1 L), and dried under vacuum at 100 °C to obtain 197.3 g (94%) of fine light-yellow crystals. Melting point: 188.1 °C. ^{1}H NMR (DMSO-d_6, D_2O) δ 4.82 (s, 3H), 4.55 (s, 2H), 7.2 (m, 3H). MS (ES) *m/z*: 225.1 $[M-H]^-$Anal. Calcd for $C_{10}H_{10}O_6$: C, 53.10; H, 4.46; O, 42.44. Found: C, 53.23; H, 4.43; O, 42.41

7-Methoxy-3-acetoxybenzofuran (**10**): A well-agitated mixture of acetic anhydride (950 mL), acetic acid (140 mL), anhydrous sodium acetate (108 g), and **9** (190.0 g, 0.84 M) was heated to reflux (125 °C) for 3.75 hours. The mixture was then cooled to 60 °C in an ice/water bath, and water (220 mL) added at such a rate that the temperature remained between 38 and 70 °C during the addition. The mass was cooled to room temperature, and held overnight. Additional water (2.30 L) was then added over 1.5 hours to precipitate a thick mass of crystals. After stirring an additional 1.5 hours, the product was collected by filtration, washed well with water (4 L), and dried under vacuum at 45 °C to obtain 149.3 g (86%) of fine golden-yellow crystals. Melting point: 70.4 °C. ^{1}H NMR (DMSO-d_6) δ 2.38 (s, 3H), 3.95 (s, 3H), 7.0 (d, 1H), 7.15 (d, 1H), 7.23 (t, 1H), 8.19 (s, 1H). MS (ES) *m/z*: 207.4 $[M+H]^+$ Anal. Calcd for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89; O, 31.04. Found: C, 64.07; H, 4.87; O, 31.03.

7-Methoxy-3(2H)-benzofuranone (**1**): A mixture of **10** (140.5 g, 0.68 M), methanol (1120 mL), water (600 mL) and 1 N HCl (210 mL) was heated to reflux (75 °C) for 3.5 hours. The mixture was cooled to 65 °C, and stirred with Darco® G-60 activated carbon (20 g) for 10 minutes. After filtering hot, the mixture was stirred at room temperature overnight. Water (1000 mL) was then added over 45 minutes to precipitate additional product. After cooling to 2-5 °C for 1 hour, the

product was collected by filtration, washed with water, and dried under vacuum at 50 °C to obtain 88.4 g (79%) of coarse light-orange crystals. Melting point: 81.4 °C, (Lit[5] mp 83-84).^{1}H NMR (DMSO-d_6) δ 3.9 (s, 3H), 4.82 (s, 2H), 7.07 (t, 1H), 7.19 (d, 1H), 7.36 (d, 1H). MS (ES) *m/z*: 165.4 $[M+H]^+$ Anal. Calcd for $C_9H_8O_3$: C, 65.85; H, 4.91; O, 29.24. Found: C, 65.82; H, 4.95; O, 29.30.

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