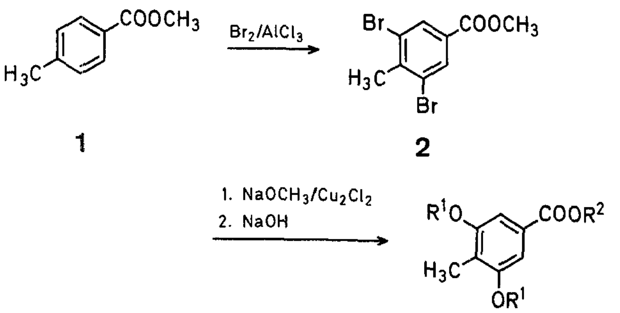
A Convenient Synthesis of 3,5-Dimethoxy-4-methylbenzoic Acid

Percy S. MANCHAND*, John M. TOWNSEND, Peter S. BELICA, Harry S. WONG

Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110, U.S.A.

3,5-Dihydroxy-4-methylbenzoic acid (5) has been used in the synthesis of certain fungal metabolites, e.g., sclerotiorin[1] and mitorubrin[2]. Except for a recent synthesis by Briggs and Whalley[3], previous syntheses[4,5,6,7] of this relatively simple acid and of its dimethyl ether 4 have been fraught with considerable difficulties, giving the product, often of poor quality, in low and variable yields. Briggs and Whalley's synthesis[3] starts from 3,4,5-trimethoxybenzoic acid, which is subjected to a Birch reduction to give 1,4-dihydro-3,5-dimethoxybenzoic acid. *O*-Demethylation of the latter with acid followed by *C*-methylation with methyl iodide, bromination, and dehydrobromination (using Raney nickel) then gave the final product in ~35% overall yield.

Sometime ago, we required substantial quantities of 3,5-dimethoxy-4-methylbenzoic acid (4) and decided that an experimentally less demanding synthesis of 4 would be desirable. In the present communication, we describe a simple synthesis of 4 in 52% yield from methyl 4-methylbenzoate (1), as outlined below.



3 $R^1, R^2 = CH_3$
4 $R^1 = CH_3, R^2 = H$
5 $R^1, R^2 = H$

Bromination of methyl 4-methylbenzoate (1) with bromine in the presence of aluminum chloride gave the dibromide 2 in an unoptimized yield of 65%; the bromination was unsuccessful in the absence of a Lewis acid. Treatment of a pyridine solution of 2 with sodium methoxide in the presence of copper(I) chloride[8] afforded 3, which was then hydrolyzed to give the acid 4. The use of the free acid in the exchange of methoxide for bromide was unsuccessful.

Methyl 4-Methylbenzoate (1):

A stirred solution of 4-methylbenzoic acid (272 g, 2 mol) in methanol (1.5 l) is treated dropwise with concentrated sulfuric acid (100 ml). The mixture is boiled under reflux for 18 h, concentrated to 1 l, poured into water (1.5 l), and extracted with ether (3 × 1 l). The extract is washed with saturated brine, dried with magnesium sulfate, and evaporated to give crude 1 (302 g) which is distilled; yield: 285 g (95%); b.p. 72–73 °C/1.5 torr.

$C_9H_{10}O_2$	calc.	C 71.98	H 6.71
(150.1)	found	71.78	6.98

M.S.: $m/e = 150$ (M^{+}, 75).

I.R. ($CHCl_3$): $\nu = 1712$; 1285; 845 cm^{-1}.

U.V. (C_2H_5OH): $\lambda_{max} = 236$ ($\varepsilon = 15560$) nm.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.33$ (s, 3H); 3.84 (s, 3H); 7.06 (d, 2H, $J = 7$ Hz); 7.77 ppm (d, 2H, $J = 7$ Hz).

Methyl 3,5-Dibromo-4-methylbenzoate (2):

Aluminum chloride (216 g, 1.60 mol) is added portion-wise, with cooling and stirring, to methyl 4-methylbenzoate (90 g, 0.6 mol). Bromine (200 g) is then added to the stirred mixture during 30 min at such a rate that the temperature of the reaction is kept below 20 °C. Stirring is continued at room temperature for 30 min and at 80–85 °C for 1 h. The mixture is cooled to 30 °C and treated with methanol (1 l) during 30 min (cooling is necessary); it is then stirred at room temperature overnight. The crude product is collected by filtration, washed with cold (0 °C) methanol (2 × 250 ml), and crystallized from methanol at 10 °C to give colorless crystals; yield: 120 g (65%); m.p. 86–88 °C.

$C_9H_8Br_2O_2$	calc.	C 35.10	H 2.62	Br 51.89
(307.8)	found	35.29	2.72	51.69

M.S.: m/e (relative intensity) = 306 (M^{+}, 100).

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I.R. (CHCl$_3$): $\nu = 1725$; 1280 cm^{-1}.

U.V. (C$_2$H$_5$OH): $\lambda_{max} = 213$ ($\varepsilon = 42800$) nm.

^{1}H-N.M.R. (CDCl$_3$): $\delta = 2.59$ (s, 3H); 3.90 (s, 3H); 7.99 ppm (s, 2H).

3,5-Dimethoxy-4-methylbenzoic Acid (4):

To a solution of sodium methoxide [from sodium (20.7 g, 0.9 mol)] in methanol (180 ml) is added methyl 3,5-dibromo-4-methylbenzoate (46.2 g, 1.5 mmol) in pyridine (75 ml) and freshly prepared anhydrous copper(I) chloride[9] (2.12 g, 0.0125 mol). The mixture, under nitrogen, is boiled under reflux for 10 h, cooled to room temperature, and filtered over Celite. The filter cake is washed with warm methanol (300 ml), and the filtrate and washing are diluted with water (100 ml). The solution is boiled under reflux for 1 h, cooled to room temperature, and diluted with saturated brine (300 ml). The mixture is extracted with ethyl acetate (300 ml), the extract is discarded, and the aqueous phase is acidified with cold (10 °C) concentrated hydrochloric acid (100 ml, pH = 3), and then extracted with ethyl acetate (3 × 200 ml). The extract is washed with saturated brine, dried with magnesium sulfate, and evaporated. Crystallization of the residue from aqueous methanol (1:2) gives **4**; yield: 24.0 g (81%); m.p. 210–216 °C.

$C_{10}H_{12}O_4$	calc.	C 61.22	H 6.16
(196.2)	found	61.46	6.20

M.S.: *m/e* (relative intensity) = 196 (M$^+$, 100).

I.R. (KBr): $\nu = 2635$; 2570; 2520; 1683; 1148 cm^{-1}.

U.V. (C$_2$H$_5$OH): $\lambda_{max} = 298$ ($\varepsilon = 2300$); 256 ($\varepsilon = 9170$); 210 ($\varepsilon = 34900$) nm

^{1}H-N.M.R. (DMSO-d_6): $\delta = 2.05$ (s, 3H); 3.83 (s, 6H); 7.13 (s, 2H); 13.0 ppm (br s, 1H).

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