2-Hydroxy-6-methylbenzoic Acid Derivatives

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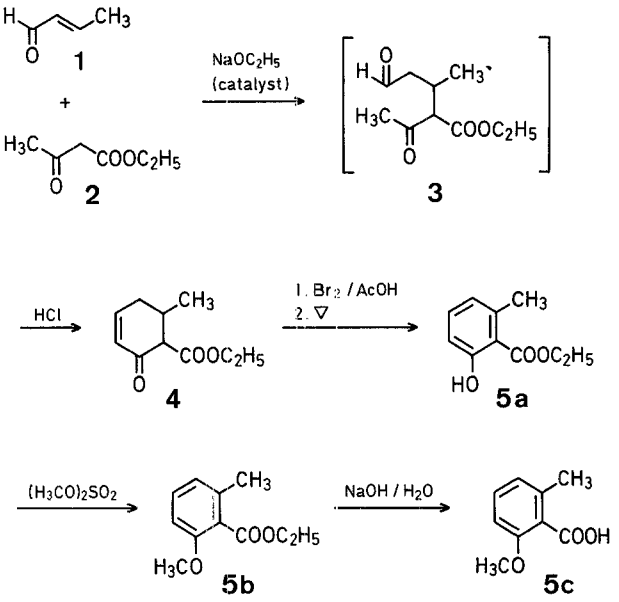
Derivatives **5a–c** of 2-hydroxy-6-methylbenzoic acid[2] are useful starting materials for natural products synthesis[3,4]. Although numerous preparations of **5a–c** have been reported[5], with few exceptions[6,7,8], they are not suitable for large scale preparation.

We have developed a procedure for preparing 100 gram quantities of **5a–c** under routine laboratory conditions. The employed sequence schematically follows two previously reported similar routes[7,8]. Through modification of reaction conditions and by using bromine to aromatize[9] cyclohexenone **4** to benzoate **5a**, not only were the yields improved, but it was possible to perform more than one step without isolation of intermediate products.



Purified crotonaldehyde (**1**)[10] was condensed with ethyl acetoacetate (**2**) in ethanol containing a catalytic amount of sodium ethoxide to afford keto-aldehyde intermediate **3**[7,8]. Without isolation and in the same flask, **3** was treated with hydrogen chloride gas to effect intramolecular cyclization to cyclohexenone **4** in 47–53% yield. Addition of bromine to **4** in acetic acid/carbon tetrachloride at 0 °C was followed by heating at reflux to eliminate hydrogen bromide and to aromatize **4** to benzoate **5a** in 82% yield. Additional manipulations of **5a** were performed. Methylation of **5a** with potassium carbonate and dimethyl sulfate in acetone afforded methyl ether **5b** in 96% yield, which on hydrolysis with aqueous sodium hydroxide, furnished 2-methoxy-6-methylbenzoic acid (**5c**) in 86% yield.

Ethyl 5-Methyl-3-oxocyclohexene-4-carboxylate (4):

To a magnetically stirred solution of sodium (1 g) dissolved in ethanol (300 ml) is added ethyl acetoacetate (**2**; 195 g, 1.5 mol). After the reaction mixture has been cooled in an ice bath, purified crotonaldehyde[10] (**1**; 105 g, 1.5 mol) in ethanol (100 ml) is added over 1 h, and the solution stirred at room temperature overnight. The yellow turbid solution is cooled in an ice bath, saturated with dry hydrogen chloride gas, and then allowed to warm to room temperature and stand overnight. [Completeness of the cyclization reaction was tested by examining the ^{1}H-N.M.R. spectrum of a sample from which the ethanol had been removed. If the spectrum showed a large singlet for the acetyl group at $\delta = 2.2$ ppm, the solution was resaturated with hydrogen chloride gas and allowed to stand for another 24 h. Although the acetyl absorption does not completely disappear, it is essential to get it as small as possible to maximize the yield of product.] The cyclohexenone **4** is isolated by evaporating the solvent at reduced pressure and vacuum distilling the residue through a short path apparatus[11]. The actual distillation is complex. The vacuum pressure is adjusted to 0.5 torr, and the flask is heated to ~50 °C at which point there is a sharp rise in pressure due to decomposition. Moderate heating is continued until the decomposition ceases (1–2 h) and the pressure returns to normal (0.5 torr). The distillation is interrupted and the trap emptied. Resumption of the distillation gives a mixture of isomers of **4**; yield: 129–139 g (47–53%); b.p. 80–95 °C/0.5 torr (Ref.[7], b.p. 90 °C/0.2 torr).

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Ethyl 2-Hydroxy-6-methylbenzoate (5a):
The above product **4** is divided in half and two preparations are conducted simultaneously.

Bromine (60 g, 0.374 mol) in acetic acid (250 ml) is added in a thin stream to a magnetically stirred solution of cyclohexenone **4** (68 g, 0.373 mol) in carbon tetrachloride (250 ml) in a 2 l flask cooled in an ice bath. After the bromine addition is complete, the solution is stirred for 30 min, and then heated under reflux for 16 h. A continuous nitrogen flow is maintained to aid in the removal of the copious quantities of escaping hydrogen bromide. The dark reaction mixture is cooled to room temperature and dichloromethane (300 ml) and water (300 ml) are added. After thorough mixing, the water layer is siphoned off. The water washing is repeated several times before a final sodium hydrogen carbonate wash to remove the residual traces of acetic acid. The organic layer is decanted in portions through a separatory funnel to remove the water which could not be removed by siphoning, then dried with sodium sulfate, and evaporated at reduced pressure below 40 °C. The products of the two bromination-dehydrobromination reactions are combined and steam distilled. Efficient cooling of both the receiver and condenser are essential in order to prevent loss of the product. The product is collected by filtration and recrystallized from methanol/water to furnish pure **5a**; yield: 110 g (82%); m.p. 42 °C (Ref.[7] m.p. 42.5 °C).

Ethyl 2-Methoxy-6-methylbenzoate (5b):
A mechanically stirred mixture of phenol **5a** (86 g, 0.48 mol), dimethyl sulfate (78 g, 0.62 mol), and anhydrous potassium carbonate (124 g, 0.90 mol) in acetone (500 ml) is heated under reflux under nitrogen. The reaction is followed by T.L.C. (silica gel/dichloromethane) and when complete, is filtered, and the acetone evaporated. Excess dimethyl sulfate is conveniently removed by dissolving the residue in ether (800 ml) and adding excess triethylamine (70 g). The ether solution becomes opaque and an oily precipitate of quarternary salt forms. After 1 h, the solution is transferred to a separatory funnel and successively washed with water (2 × 100 ml), 10% hydrochloric acid (100 ml), and finally with brine. The solution is dried with magnesium sulfate, the ether evaporated, and the residue distilled to afford pure product **5b**; yield: 89 g (96%); b.p. 89–91 °C/1 torr (Ref.[8], b.p. 80 °C/0.8 torr).

2-Methoxy-6-methylbenzoic Acid (5c):
Ester **5b** (82 g, 0.422 mol), sodium hydroxide (34 g, 0.85 mol), water (250 ml), and enough hot alcohol to make the solution homogeneous, are heated under reflux until T.L.C. analysis (silica gel/dichloromethane) shows the absence of ester (~8 h). The ethanol is removed at reduced pressure, and the water solution is acidified with concentrated hydrochloric acid. The aqueous solution is extracted with ethyl acetate (3 × 200 ml), the extract is concentrated, and the resulting benzoic acid crystals collected. Further concentration of the filtrate gives a second crop of crystals; total yield: 60.5 g (86%); m.p. 139–141.5 °C (Ref.[7], m.p. 139–141 °C).

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[2] Both 2-hydroxy-6-methylbenzoic acid and its methyl ester are naturally occurring compounds. The former is a common mold metabolite and the latter is a caste specific alarm pheromone for certain species of ants.

[3] We have extensively employed **5b** and **5c** in our natural products synthesis program. See: F. M. Hauser, R. P. Rhee, S. Prasanna, S. M. Weinreb, J. H. Dodd, *Synthesis* **1980**, 72, and references therein.

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[9] For the use of bromine to aromatize acetyl substituted cyclohexenones see: R. N. Lacey, *J. Chem. Soc.* **1960**, 1625.

[10] Commercial crotonaldehyde containing 15% water was cooled in a freezer at −20 °C then filtered to remove the water crystals. Subsequent distillation of the filtrate afforded pure crotonaldehyde.

[11] The product at this point is probably the hydrogen chloride adduct of **4**.

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