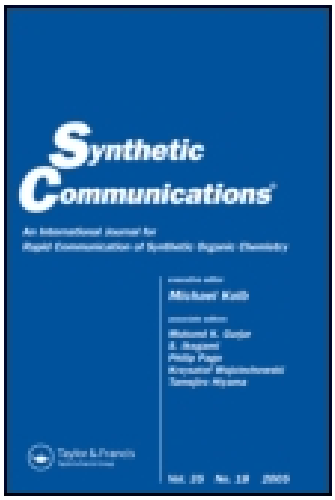

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A PRACTICAL AND CONVENIENT SYNTHESIS OF METHYL 5-FORMYL-3-METHOXYBENZOATE

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A PRACTICAL AND CONVENIENT SYNTHESIS OF METHYL 5-FORMYL-3-METHOXYBENZOATE

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ABSTRACT

A practical and convenient synthesis of methyl 5-formyl-3-methoxybenzoate starting from 3-hydroxy-5-(methoxycarbonyl)benzoate in 65% overall yield is described. Ethyl 5-formyl-3-methoxybenzoate was also prepared in the similar manner.

A number of marketed pharmaceuticals possess a hydroxy benzoic acid moiety as a substructure. For examples, these structures are present in the platelet antiaggregatory agent triflusal, the antihypertensive agent reserpine and the antiarthritic agent mycophenolate mofetil as well as the analgesic and anti-inflammatory agent aspirin. As part of our drug discovery effort in the area of anti-inflammatory agents, we designed several isomeric hydroxy 3-benzoic acid derivatives. The 4-hydroxy derivatives (**1**, Figure 1) were prepared starting from methyl 5-formylsalicylate (**2**).[1] In order to prepare the isomeric 5-hydroxy-3-benzoic acid derivatives (**3**) in a similar fashion, we required a source of methyl 5-formyl-3-methoxybenzoate (**4**).

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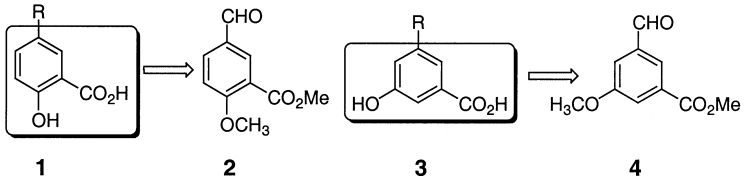
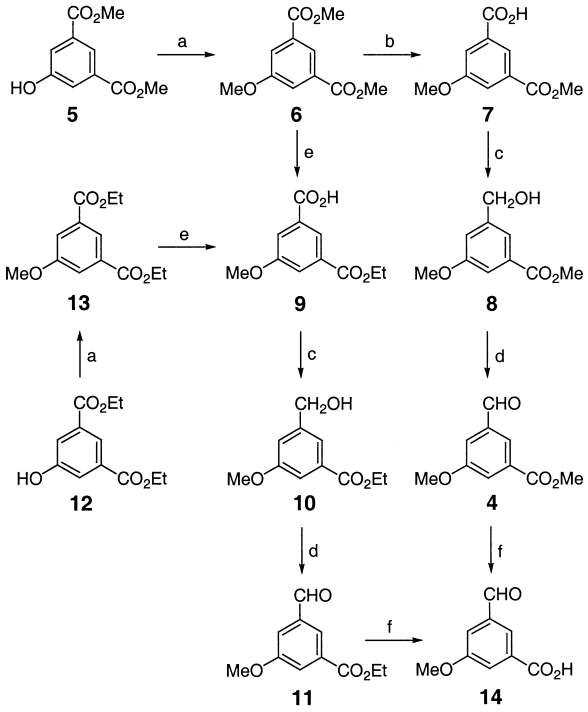


Figure 1.

A search of the chemical literature revealed only a single report of the preparation of **4**,[2] which was accomplished by the selective reduction of methyl 3-methoxy-5-(methoxycarbonyl)benzoate **6** with DIBAL-H. No information about yield and physical data were provided within this citation, however. After attempts at reproducing this procedure proved troublesome, we sought an alternative strategy. We herein report a new practical



Scheme 1. **Reagents**: a. MeI, K_2CO_3, Acetone; b. KOH, MeOH/THF; c. i) $BH_3{\cdot}(CH_3)_2S$, THF; ii) H_2O/HOAc; d. MnO_2, EtOAc; e. KOH, EtOH/THF; f. i) LiOH, MeOH/H_2O; ii) HCl

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and convenient synthesis of compound **4** from 3-hydroxy-5-(methoxycarbonyl)benzoate **5** in 65% overall yield in four steps without column chromatography (Scheme 1). The strategy is also applicable to the preparation of ethyl 5-formyl-3-methoxybenzoate **11** from either **5** or ethyl 5-(ethoxycarbonyl)-3-methoxybenzoate **13**.

3-Hydroxy-5-(methoxycarbonyl)benzoate **5** was treated with iodomethane and potassium carbonate to yield methoxy compound **6**, which was then selectively hydrolyzed in the presence of 0.9 equivalent powder potassium hydroxide in methanol/THF to give mono acid **7** in high yield. When **7** was treated with borane dimethyl sulfide complex, the carboxylic acid group was selectively reduced in the presence to the ester group. The resulting alcohol **8** was oxidized to methyl 5-formyl-3-methoxybenzoate **4** using activated MnO_2 in ethyl acetate. If ethanol was used instead of methanol during the hydrolysis of diester **6** in order to increase the refluxing temperature, a transesterification occurred to generate compound **9**, which could also be prepared starting from ethyl 5-(ethoxycarbonyl)-3-hydroxybenzoate **12**[3] following the same procedures. Compound **9** was oxidized to provide ethyl 5-formyl-3-methoxybenzoate **11**. Finally, compounds **4** and **11** were converted to acid **14** by treatment with lithium hydroxide in methanol and water.

In conclusion, practical and convenient syntheses of methyl 5-formyl-3-methoxybenzoate and ethyl 5-formyl-3-methoxybenzoate were achieved in good overall yield without column chromatography. These two compounds can be used as alternative building blocks to methyl 5-formylsalicylate in medicinal and combinatorial chemistry research.

EXPERIMENTAL

Melting points were determined on a Mel Temp II melting point apparatus and uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 1600 Fourier-transformed-infrared spectrometer. ^{1}H NMR data were obtained on a Varian Gemini-400 spectrometer (300 MHz). Chemical shifts are given in ppm on the δ scale from TMS. Atmosphere pressure chemical ionization mass spectra (APCIMS) were acquired with a Sciex API150 mass spectrometer under the control of a Sciex masschrom 1.0 data system. Elemental analyses were obtained from Robertson Microlit Laboratories Inc., Madison, NJ, and are within 0.4% of theoretical values. Anhydrous solvents were obtained commercially and used without further drying.

Methyl 3-methoxy-5-(methoxycarbonyl)benzoate (6): To a solution of methyl 3-hydroxy-5-(methoxycarbonyl)benzoate **5** (29 g, 138 mmol) in acetone (200 mL) was added anhydrous potassium carbonate (23 g, 166 mmol)

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and iodomethane (39.2 g, 276 mmol). The mixture was heated at reflux under N_2 overnight. After cooling to room temperature, the solids were filtered through celite and washed with acetone. The filtrate was concentrated and redissolved in ether, washed with 1 N HCl, saturated $NaHCO_3$, and brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by crystallization from ether/hexane to give the title compound **5** (29.5 g, 95%) as a white solid: mp 110–112 °C; IR (KBr) 2958, 1730, 1593, 1440, 1269, 1053, 762 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.87 (s, 3H), 3.96 (s, 6H), 7.72 (d, $J = 1.2$ Hz, 2H), 8.25 (d, $J = 1.2$ Hz, 1H); LC-MS (m/z) 225 (M+1); Anal. Calcd. for $C_{11}H_{12}O_5$: C, 58.93; H, 5.39. Found: C, 59.13; H, 5.38.

Ethyl 5-(ethoxycarbonyl)-3-methoxybenzoate (13): This compound was prepared from ethyl 5-(ethoxycarbonyl)-3-hydroxybenzoate **12** in the similar manner as described above for the preparation of compound **6** and purified by Kugelrohr distillation to afford the title compound **13** (96%) as a colorless oil: IR (neat) 2982, 1725, 1600, 1460, 1315, 1265, 1107, 1054, 758 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (t, $J = 7.2$ Hz, 6H), 3.89 (s, 3H), 4.40 (q, $J = 7.2$ Hz, 4H), 7.75 (d, $J = 1.2$ Hz, 1H), 8.18 (t, $J = 1.2$ Hz, 2H); LC-MS (m/z) 253 (M+1); Anal. Calcd. for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39. Found: C, 61.71; H, 6.19.

3-Methoxy-5-(methoxycarbonyl)benzoic acid (7): Powdered potassium hydroxide (85%, 3.56 g, 54 mmol) was added portionwise to a solution of methyl 3-methoxy-5-(methoxycarbonyl)benzoate **6** (14.3 g, 60 mmol) in anhydrous methanol (90 mL) and anhydrous THF (60 mL) over 10 min with stirring. The mixture was stirred at room temperature for 1 h and then heated at reflux for additional 6 h. After removal of the solvents under reduced pressure, the thick slurry was dissolved in water (300 mL) and washed with CH_2Cl_2. Concentrated HCl was added to the aqueous phase to pH ~ 3. The resulting white precipitate was collected by vacuum filtration and dried in vacuo to give the title compound **7** (10.46 g, 83%) as a white solid: mp 186–188° C; IR (KBr) 1731, 1693, 1597, 1423, 1318, 1273, 1122, 1057, 754 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.84 (s, 3H), 3.85 (s, 3H), 7.61 (m, 1H), 7.63 (m, 1H), 8.04 (m, 1H); LC-MS (m/z) 211 (M+1), 209 (M−1); Anal. Calcd. for $C_{10}H_{10}O_5$: C, 57.14; H, 4.80. Found: C, 57.00; H, 4.78.

5-(Ethoxycarbonyl)-3-methoxybenzoic acid (9): This compound was prepared either from methyl 3-methoxy-5-(methoxycarbonyl)benzoate **6** in 81% yield or ethyl 5-(ethoxycarbonyl)-3-methoxybenzoate **13** in 82% yield using absolute ethyl alcohol and anhydrous THF as solvents in the similar manner as described above for the preparation of compound **7** to give the title compound **9** as a white solid: mp > 300 °C; IR (KBr) 3478, 2981, 1712, 1553, 1404, 1294, 1055, 766 cm^{-1}; ^1H NMR (DMSO-d_6)

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δ 1.32 (t, $J = 7.2$ Hz, 3H), 3.84 (s, 3H), 4.31 (q, $J = 7.2$ Hz, 2H), 7.60 (m, 1H), 7.63 (m, 1H), 8.03 (m, 1H), 13.32 (s, 1H); LC-MS (*m*/*z*) 225 (M+1), 223 (M−1).

Methyl 5-(hydroxymethyl)-3-methoxybenzoate (8): $BH_3 \cdot (CH_3)_2S$ complex (2.0 M in THF, 24 mL, 48 mmol) was added dropwise to a solution of 3-methoxy-5-(methoxycarbonyl)benzoic acid **7** (8.4 g, 40 mmol) in anhydrous THF (40 mL) under argon at 0°C over 30 min. The mixture was then heated at 60°C overnight. The reaction was quenched and neutralized by addition of 1:2 H_2O/glacial acid (6 mL). After removing the solvents, the thick slurry was dissolved in EtOAc, washed with 30% K_2CO_3, 1N HCl, saturated $NaHCO_3$, brine, and dried over anhydrous Na_2SO_4. The solution was then filtered through silica gel with a Buchner funnel and concentrated to give the title product **8** (7.04 g, 90%) as a colorless oil: IR (neat) 3417(br s), 2950, 1712, 1602, 1460, 1332, 1056, 873, 768 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.85 (s, 3H), 3.91 (s, 3H), 4.41 (s, 2H), 7.13 (m, 1H), 7.47 (m, 1H), 7.61 (m, 1H); LC-MS (*m*/*z*) 197 (M+1).

Ethyl 5-(hydroxymethyl)-3-methoxybenzoate (10): This compound was prepared from 5-(ethoxycarbonyl)-3-methoxybenzoic acid **9** in 90% yield in the same manner as described above for the preparation of compound **8** to give the title compound **10** as a colorless oil: IR (neat) 3416 (br s), 2939, 1714, 1600, 1461, 1306, 1056, 868, 7770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (t, $J = 7.2$ Hz, 3H), 3.86 (s, 3H), 4.37 (q, $J = 7.2$ Hz, 2H), 4.72 (s, 2H), 7.13 (m, 1H), 7.48 (m, 1H), 7.62 (m, 1H); LC-MS (*m*/*z*) 211 (M+1).

Methyl 5-formyl-3-methoxybenzoate (4): To a solution of methyl 5-(hydroxymethyl)-3-methoxybenzoate **8** (5.88 g, 30 mmol) in EtOAc (200 mL) was added activated MnO_2 (85%, 12.5 g, 128 mmol). The reaction mixture was heated under reflux for 5 h. After cooling to room temperature, the mixture was filtered through celite and the filtrate concentrated. The residue was purified by crystallization from ether/hexane to give the title compound **4** (5.29 g, 91%) as a white solid: mp 60–61°C; IR (KBr) 2354, 1720, 1593, 1445, 1389, 1106, 1058, 764 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.91 (s, 3H), 3.96 (s, 3H), 7.58 (dd, $J = 1.2$ Hz, 1H), 7.82 (dd, $J = 1.2$ Hz, 1H), 7.61 (dd, $J = 1.2$ Hz, 1H), 10.02 (s, 1H); LC-MS (*m*/*z*) 195 (M+1); Anal. Calcd. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.139. Found: C, 62.03; H, 5.28.

Ethyl 5-formyl-3-methoxybenzoate (11): This compound was prepared from ethyl 5-(hydroxymethyl)-3-methoxybenzoate **10** in 92% yield in the same manner as described above for the preparation of compound **4** to give the title compound **11** as a colorless oil: IR (neat) 2980, 1696, 1599, 1455, 1387, 1331, 1227, 1055, 873, 768 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (t, $J = 7.2$ Hz, 3H), 3.90 (s, 3H), 4.41 (q, $J = 7.2$ Hz, 2H), 7.57 (dd, $J = 1.2$ Hz, 1H), 7.2 (dd, $J = 1.2$ Hz, 1H), 8.11 (t, $J = 1.2$ Hz, 1H),

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10.02 (s, 1H); LC-MS (*m*/*z*) 209(M+1); Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.49; H, 5.87.

5-Formyl-3-methoxybenzoic acid (14): To a solution of methyl 5-formyl-3-methoxybenzoate **4** (194 mg, 1 mmol) in methanol and water (8 mL, v/v = 3/1) was added lithium hydroxide monohydrate (82 mg, 2 mmol). The mixture was stirred at room temperature overnight and the most of methanol was removed under reduced pressure. The aqueous solution was diluted to 15 mL and washed with CH_2Cl_2. Concentrated HCl was added to neutralize the solution until pH $\sim$ 3. The product was collected by vacuum filtration and dried in vacuo to give the title compound **14** (170 mg, 94%) as a white solid: mp 234–236°C; IR (KBr) 2371, 1691, 1281, 1182, 869, 749 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.87 (s, 3H), 7.63 (dd, J = 1.2 Hz, 1H), 7.69 (dd, J = 1.2 Hz, 1H), 8.02 (dd, J = 1.2 Hz, 1H), 10.02 (s, 1H), 13.37 (s, 1H); LC-MS (*m*/*z*) 179 (M−1). The title compound **14** was also prepared from ethyl 5-formyl-3-methoxybenzoate **11** in 92% yield in the same manner.

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