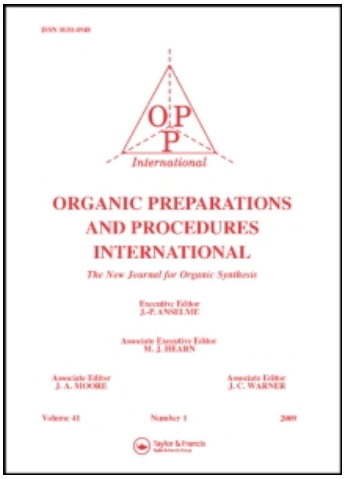

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A CONVENIENT PREPARATION OF METHYL 4-(2-AMINOETHYL)BENZOATE

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A CONVENIENT PREPARATION OF METHYL 4-(2-AMINOETHYL)BENZOATE

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(05/05/00)

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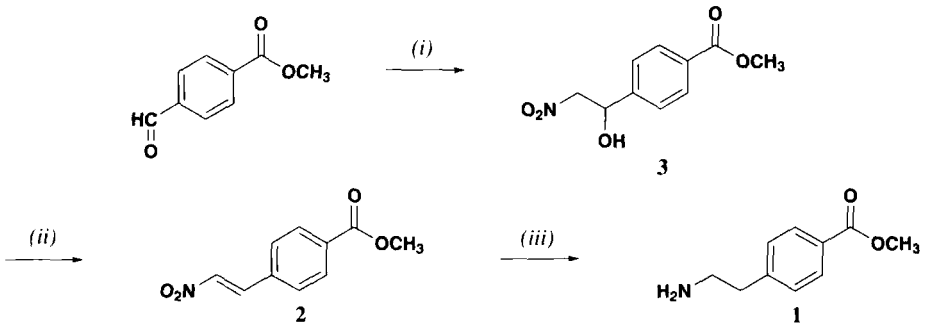
Methyl 4-(2-aminoethyl)benzoate (**1**) is an intermediate in the preparation of a variety of pharmaceuticals, including the antidiabetics Meglintide[1] and S15261,[2] the leukotriene D_4 antagonist LM-1376,[3] and the antiarteriosclerotic BM-15766.[4] It is also of value as a doubly functionalized template for the synthesis of combinatorial chemistry products. Remarkably, few preparations of **1** have been reported in the literature. These suffer from several disadvantages, including the use of starting materials that are not commercially available,[5] low yields of one or more steps, the use of

electrolytic equipment,[6] or chromatographic purification of intermediates. We reasoned that the reduction of methyl 4-(nitrovinyl)benzoate (**2**) would offer a convenient route that would be amenable to scale–up, if the reduction could be made to proceed to the saturated amine instead of to the aldehyde or oxime. Compound **2** should be readily available from methyl 4-formylbenzoate and nitromethane by the Henry reaction.[7]



i) CH_3NO_2, KOt-Bu, THF, t-BuOH. *ii)* Ac_2O, DMAP, Et_2O. *iii)* H_2, Pd-C, MeOH, HCl.

While the preparation of **2** has been described, we were unable to reproduce the published synthesis.[8] However, application of the conditions described by Denmark[9] afforded **2** cleanly and in good yield (75+%) without need for purification of the intermediate nitroaldol product **3**. Catalytic hydrogenation of **2** to afford **1** was found to proceed easily in methanol over palladium on carbon in the presence of an excess of hydrochloric acid. Other acids such as acetic acid and sulfuric acid were found to be much less effective and afforded complex mixtures.

This procedure allows the preparation of **1** to be carried out on a preparative scale to afford analytically pure **1** hydrochloride in ~60% overall yield using inexpensive commercially available reagents, without need for special equipment or chromatography.

EXPERIMENTAL SECTION

Methyl 4-formylbenzoate was obtained from Fluka (Cat. 47717). All other reagents were purchased from Fisher Scientific and were used as received. Reactions were carried out under nitrogen. Evaporations were carried out on a rotary evaporator using aspirator pressure. Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. NMR spectra were recorded on Varian Unity Inova 400 spectrometers. Mass spectra were recorded on a Hewlett Packard Model 5989 mass spectrometer using chemical ionization with ammonia. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, New York, USA.

4-(1-Hydroxy-2-nitroethyl)benzoic Acid Methyl Ester (3).- Powdered potassium t-butoxide (0.561 g, 5 mmol) was added to a solution of methyl 4-formylbenzoate (16.42 g, 100 mmol) and nitromethane (10.8 mL, 200 mmol) in 25 mL of dry THF and 25 mL of t-butanol. The reaction

mixture was stirred at 25° for 24 h, after which time tlc analysis (silica gel; 3:1 hexane-EtOAc) showed the reaction to be complete. The orange mixture was partitioned between water (200 mL) and Et_2O (200 mL). The ethereal extract was washed with saturated $NaHCO_3$, brine, dried ($MgSO_4$) and concentrated to afford 23.02 g (~100%) of crude **3** as a red oil. ^1H NMR ($CDCl_3$): δ 8.01 (d, 2 H); 7.46 (d, 2 H); 5.50 (broad d, 1 H); 4.53 (m, 2 H); 3.89 (s, 3 H). MS (NH_3 CI): *m/z* = 243 ($M + NH_4^+$).

4-(2-Nitrovinyl)benzoic Acid Methyl Ester (2).- Crude **3** (23.02 g, ~100 mmol) and DMAP (0.611 g, 5 mmol) were dissolved in 80 mL of Et_2O in a 500 mL flask fitted with a reflux condenser. Acetic anhydride (11.3 mL, 120 mmol) was added dropwise. The reaction mixture warmed to a spontaneous reflux and a precipitate began to form. The mixture was stirred at 25° overnight, at which point the reaction was complete as shown by tlc analysis (silica gel; 3:1 hexane-EtOAc). The thick mixture was filtered and the flask rinsed with additional Et_2O. The filter cake was suspended in MeOH and filtered again, then the damp filter cake was dissolved in $CHCl_3$ (500 mL). The $CHCl_3$ solution was dried ($MgSO_4$) and evaporated. The residue was slurried in hot MeOH, cooled and filtered to yield 16.27 g (78%) of **2**, mp 182-183°, *lit.*[10] mp 178-179°. ^1H NMR ($CDCl_3$): δ 8.10 (d, 2 H); 8.01 (d, J = 13.7 Hz, 1 H); 7.60 (overlapping d, 3 H); 3.94 (s, 3 H). MS (NH_3 CI): *m/z* = 225 ($M + NH_4^+$).

Anal. Calcd for $C_{10}H_9NO_4$: C, 57.97; H, 4.38; N, 6.76. Found: C, 58.10; H, 4.33; N, 6.61

4-(2-Aminoethyl)benzoic Acid Methyl Ester (1).- A suspension of 12.13 g (58 mmol) of **2** and 1.45 g of 5% palladium on carbon catalyst in 580 mL of MeOH and 24 mL of concentrated hydrochloric acid was hydrogenated in a 2 liter Parr reaction bottle until hydrogen uptake ceased. Complete reduction required approximately 3 h. The reaction mixture was filtered and evaporated to dryness. The residue was slurried in EtOAc containing 5% 2-propanol, filtered and dried to afford 9.57 g (76%) of **1** (as hydrochloride) as white crystals, mp 227–229°, *lit.*[11] mp 228-229°. ^1H NMR (CD_3OD): δ 7.99 (d, 2 H); 7.41 (d, 2 H); 3.89 (s, 3 H); 3.21 (t, 2 H); 3.04 (t, 2 H). MS (NH_3 CI): *m/z* 180 ($M + H^+$).

Anal. Calcd for $C_{10}H_{13}NO_2 \cdot HCl$: C, 55.69; H, 6.54; N 6.49. Found: C, 55.47; H, 6.66; N 6.33

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7. Methyl 4-formylbenzoate is commercially available at reasonable cost from Fluka ($0.44 per gram). Other suppliers are considerably more expensive. Alternatively, it may be prepared from 4-formylbenzoic acid, a by-product of terephthalic acid manufacture, by esterification with dimethyl sulfate.

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AN EFFICIENT AND FACILE PREPARATION OF 2,2',4,4'-TETRABROMODIPHENYLAMINE

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2,2',4,4'-Tetrabromodiphenylamine (**1**) and its N-alkyl derivatives (available by alkylation of 2,2',4,4'-tetrabromodiphenylamine) are important intermediates for the synthesis of phenazasiline compounds which possess excellent high-temperature stability coupled with antioxidant activity; these properties make them useful as antioxidants for high-temperature lubricants.[1] 2,2',4,4'-Tetrabromodiphenylamine and its N-alkyl derivatives themselves have also been used as fireproofing agents for plastics.[2]