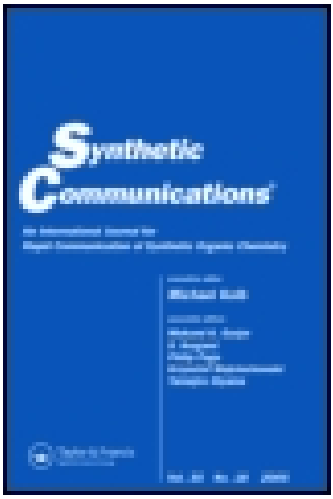

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AN EFFICIENT SYNTHESIS OF 2-(((9-FLUORENYL-METHOXYCARBONYL)AMINO)METHYL)BENZOIC ACID

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Abstract: An efficient, two-step syntesis of the title compound **3** in 61% overall yield is presented. The synthesis involves hydrazine removal of the *N*-phthalimide protecting group of α-phthalimido-*o*-toluic acid (**6**), followed by *N*-Fmoc formation with (9-fluorenylmethyl)succinimidyl carbonate.

In connection with our combinatorial chemistry program, we desired to have *N*-Fmoc-protected (aminomethyl)benzoic acid at the *para*, *meta* and *ortho* position (i.e., **1**, **2** and **3**, respectively) as building blocks. A literature survey indicated that **1**[1] and **2**[2] had been previously reported; but **3** has not. In this communication, we wish to report an efficient synthesis of **3**.

We envisioned that **3** may be derived from the Fmoc-formation of 2-(aminomethyl)benzoic acid (**4**). To our surprise, very little on the synthesis of **4** has been documented. It was prepared in a poor yield

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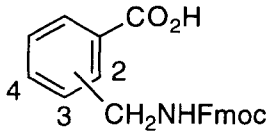
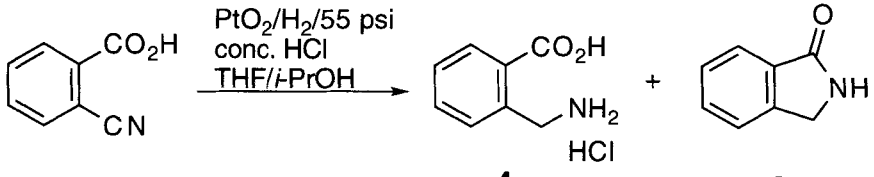


1, 4- (*para*);
2, 3- (*meta*);
3, 2- (*ortho*).

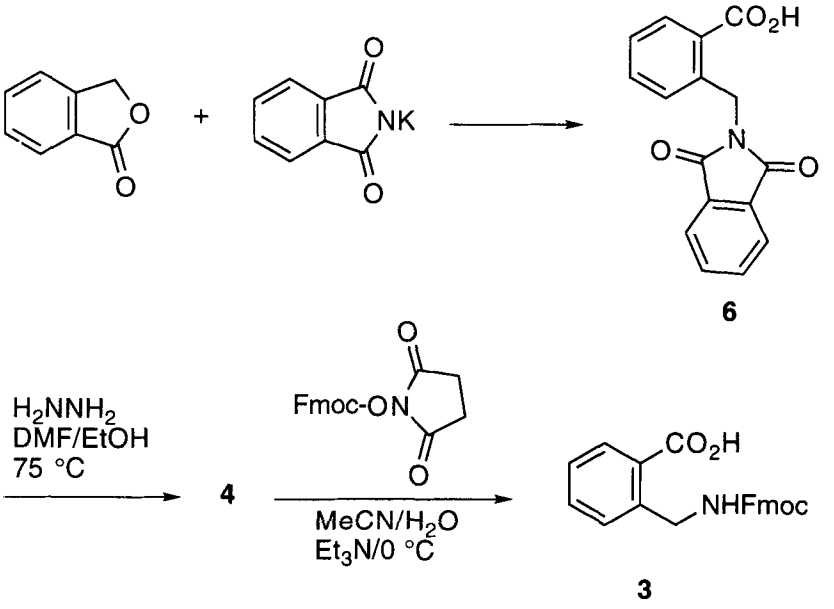
by the Hoffman rearrangement of 2-(carbamoylmethyl)benzoic acid.[3] It was also prepared by hydrolysis of phthalimidine (**5**)[4] or reduction of 2-cyanobenzoic acid,[5] but neither reaction conditions nor yields of the product was provided. Reduction of 2-cyanobenzoic acid was attempted because of readily available starting material.[6] We found that catalytic hydrogenation of 2-cyanobenzoic acid with platinum oxide in the presence of concentrated hydrochloric acid in THF/isopropanol (1:1) gave **4** in 25-35% yield.[7] The low yield is attributed to the formation of phthalimidine (**5**), derived from intramolecular cyclization of **4** with concomitant loss of water. Because of the poor yield of **4** and the cost of 2-cyanobenzoic acid and platinum (IV) oxide,[8] an alternate synthesis of **4** was pursued.



4 **5**

α-Phthalimido-*o*-toluic acid (**6**) has been prepared by reaction of phthalide and potassium phthalimide as reported.[9] The *N*-

phthalimide protecting group in **6** was then removed with hydrazine in DMF/EtOH at 80 °C to give **4** in 90% yield. Subsequent reaction of **4** with (9-fluorenylmethyl)succinimidyl carbonate in water in the presence of triethylamine furnished **3** in 68% yield after recrystallization from DMF/CH_3CN (1:8).



In summary, an efficient, two-step synthesis of **3** from **6** in 61% overall yield is presented. We are investigating the use of **3** to build combinatorial libraries, which will be reported in due course.

Experimental Section

Commercial reagents were used as received without additional purification. Melting points were uncorrected. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded using

tetramethylsilane as an internal standard. Elemental analysis was performed by Quantitative Technology, Inc., Bound Brook, NJ.

2-(Aminomethyl)benzoic Acid Hydrochloride (4)

Method A: from 2-cyanobenzoic acid

A solution of 2-cyanobenzoic acid (8.0 g, 54.4 mmol) in THF (120 mL) and isopropanol (120 mL) was added platinum oxide (650 mg, 2.86 mmol) and concentrated HCl (9 mL). The mixture was hydrogenated at room temperature at 55 psi for 24 h. After completion of the reaction, the precipitated products and catalyst were collected on a filter and washed with THF (100 mL). The filtrate, which contains phthalimidine (**5**), was kept separate. The remaining solids on the filter were then washed with methanol (150 mL). The solvent in the methanol filtrate was evaporated to dryness to give 3.6 g (35% yield) of **4** as a white solid, mp 202-204 °C. The spectral data are identical to those reported in Method B (see below).

Method B: from α-phthalimido-*o*-toluic acid (6)

A mixture of α-phthalimido-*o*-toluic acid (**6**)[9] (7.0 g, 24.9 mmol) in 55 mL of DMF and 110 ml of ethanol was heated to 75 °C to become a clear solution. To this was added hydrazine (1.2 g, 37.5 mmol) dropwise. The reaction solution was heated at 75 °C for 2 h. After cooling to 0 °C, the precipitated phthalhydrazide was removed by filtration. The solvent in the filtrate was evaporated. The remaining residue was treated with 50 mL of 1N HCl and the aqueous mixture stirred for 2 h. More precipitated phthalhydrazide was filtered off. The solvents in the filtrate were evaporated, dried to

give 4.2 g (90% yield) of **4**; mp 207-208 °C (*lit.* 217-218 °C).[5] ^{1}H NMR (DMSO-d_6) δ 8.49 (br, 3H), 7.94 (d, 2H, J = 7.7 Hz), 7.59-7.43 (m, 3H), 4.22 (s, 2H). ^{13}C NMR (DMSO-d_6) δ 137.42, 131.71, 131.42, 131.20, 130.52, 129.81, 43.18. MS (ESI) 174 (M+Na, 7), 152 (M+H, 100). HRMS (NH_3/CI) Calcd. for $C_8H_{10}NO_2$: 152.0711; Found: 152.0716. IR (KBr) 3148, 3000-2500 (br), 1694, 1632, 1604, 1584, 1554, 1458, 1400, 1374, 1070, 754, 712 cm^{-1}.

2-(((9-Fluorenylmethoxycarbonyl)amino)methyl)benzoic Acid (3)

A solution of **4** (3.0 g, 16 mmol) in 30 mL of water was cooled to 0 °C and triethylamine (2.5 mL, 18 mmol) was added. It was noted that the reaction temperature raised to 7 °C, and pH of the solution changed from 2 to 9. The reaction solution was cooled back to 0 °C and then added a solution of 9-(fluorenylmethyl)succinimyl carbonate (5.4 g, 16 mmol) in 90 mL of acetonitrile slowly and pH of the reaction solution was adjusted to about 8 by adding additional triethylamine (2.1 g). The reaction solution was stirred for 1 h. The solvents in the solution were evaporated to a white slurry, which was treated with 200 mL of 1N HCl. After stirring for 30 min, the precipitates were collected on a filter, washed with cold 1N HCl and ether, and dried to give 4.89 g (82% yield) of crude **3**. This was recrystallized from 180 mL of DMF/CH_3CN (1:8) to give 4.06 g (68% yield) of pure **3** as a white solid; mp 205-207 °C. ^{1}H NMR (DMSO-d_6) δ 13.00 (br, 1H), 7.86 (d, 3H, J=7.3 Hz), 7.81-7.68 (m, 3H), 7.50 (t, 1H, J=7.3 Hz), 7.41-

7.28 (m, 6H), 4.55 (d, 2H, *J*=5.9 Hz), 4.36 (d, 2H, *J*=6.6 Hz), 4.22 (t, 1H, *J*=6.4 Hz). ^{13}C NMR (DMSO-d_6) δ 168.79, 156.82, 144.32, 141.27, 141.22, 132.43, 130.81, 129.66, 128.03, 127.64, 127.49, 127.11, 125.60, 120.53, 65.76, 47.30, 42.75. MS(ESI) 374 (M+H, 100). HRMS (NH_3/CI) Calcd. for $C_{22}H_{20}NO_4$: 374.1392; Found: 374.1400. IR (KBr) 3304, 2974-2654 (br), 1692, 1554, 1284, 1264, 1140, 774, 734 cm^{-1}. Anal. Calcd for C, 73.98, H, 5.14, N, 3.75; Found C, 73.87, H, 5.09, N, 3.71.

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6. 2-Cyanobenzoic acid was prepared from phthalic anhydride in 3 steps (see reference 5).
7. Under the same reaction conditions, 3-cyanobenzoic acid and 4-cyanobenzoic acid were reduced to 3-aminobenzylamine and 4-aminobenzylamine hydrochloride in 70% and 75% yield, respectively.
8. Platinum oxide can be purchased from Aldrich for $291.40/ 5 grams; 2-cyanobenzoic acid is available from ICN for $92.50/10 grams.
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