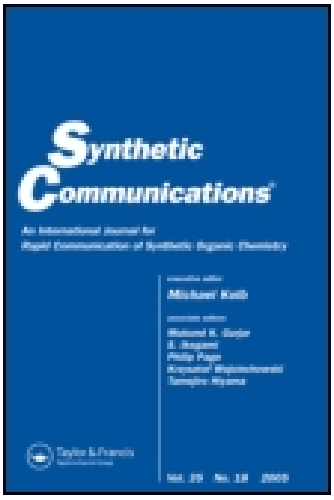

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A Scaleable Method for Preparing 3-Fluorenylmethoxycarbonylamino-5-hydroxybenzoic Acid

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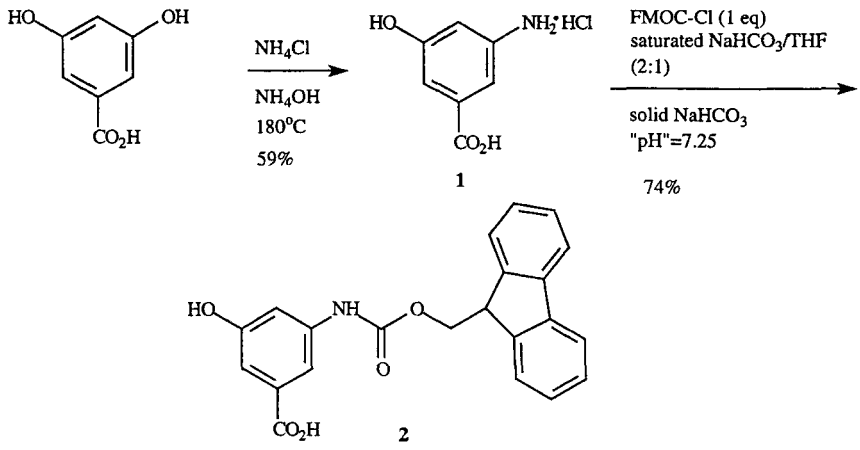
Abstract: A scaleable synthesis of 3-fluorenylmethoxycarbonylamino-5-hydroxybenzoic acid is described.

Introduction:

A wide variety of structures can be prepared through combinatorial application of standard amide and Mitsunobu coupling methods and various scaffolds have been exploited in this fashion. One such scaffold, 3-amino-5-hydroxybenxoic acid hydrochloride **1,** has been used by others[1] and at Selectide[2] for library production. It was found that protection of the aniline nitrogen, although not necessary, allowed more flexibility in the chemistry, eleviated side reactions and resulted in cleaner chemistry. For this reason, an efficient method for preparing of 3-fluorenylmethoxycarbonylamino-5-hydroxybenzoic acid **2** was desired. The following describes a scaleable preparation of 3-fluorenylmethoxycarbonylamino-5-hydroxybenzoic acid **2** in an overall 44% yield with full, previously unpublished analytical data.

Scheme 1:



Discussion:

Treatment of 3,5-dihydroxybenzoic acid with ammonium chloride and ammonium hydroxide in a steel autoclave at elevated temperature prepared the 3-amino-5-hydroxybenzoic acid hydrochloride **1**.[1b,c] Purification of **1** by recrystallization from 6M HCl afforded 3-amino-5-hydroxybenzoic acid hydrochloride **1** in a 59% overall yield in high purity. The amino group was protected with 9-fluorenylmethyl chloroformate (FMOC-Cl) under aqueous conditions to give the desired 3-fluorenylmethoxycarbonylamino-5-hydroxybenzoic acid **2** in 74% yield. This reaction was run in saturated aqueous sodium bicarbonate and tetrahydrofuran (2:1 ratio) at ambient temperature. It was crucial to keep the measured pH at 7.25. If the pH went below 7, the coupling would not proceed; above a pH of 8, the base sensitive FMOC protecting group would be destroyed. The observed pH was very easily buffered by the addition of solid sodium bicarbonate to maintain a saturated environment.

Conclusion:

These sensitive protecting conditions proved to be an efficient method for preparing the desired 3-fluorenylmethoxycarbonylamino-5-hydroxybenzoic acid **2** in large quantities. Full analytical data are disclosed.

General

NMR spectra were recorded on a Varian XL 300 and/or Varian GEMINI-300 spectrometers at 300 MHz for ^{1}H and 75 MHz for ^{13}C. Elemental analysis were performed by Robertson Microlit, Inc. Madison NJ. Spectral analyses were performed by the Analytical and Structural Sciences Department, Hoechst Marion Roussel Research Institute, Cincinnati Center.

Experimental:

3-Amino-5-hydroxybenzoic acid hydrochloride (1): 3,5-Dihydroxybenzoic acid (250 g, 1.62 mol), ammonium chloride (212.5 g, 3.97 mol), and concentrated ammonium hydroxide (750 mL) were charged to a 2 L autoclave. The apparatus was sealed and the mixture was stirred and heated at 180 °C for 40 h (resulting pressure 120 psi). The reaction was cooled and evaporated to dryness at 50 °C/ 50 torr. The residue was dissolved into 6N HCl (10 L), heated at reflux for 20 h, cooled, and concentrated at 50 °C/ 50 torr to a volume of 3 L. The solid that formed was filtered and air dried. This solid was dissolved into hot 6N HCl (4 L) and treated with charcoal (25 g). The charcoal was filtered off while hot through celite and when the filtrate cooled, solid formed. The solid was collected on a filter, washed with 6N HCl (500 mL), and air dried to give 180 g of 3-amino-5-hydroxybenzoic acid hydrochloride **1** in 59% yield. ^{1}H NMR (DMSO) δ 7.49 (s, 1 H), 7.48 (s, 1 H), 7.05 (s, 1 H); ^{13}C NMR (DMSO) ppm 166.5, 158.6, 133.4, 133.3, 115.7, 114.5, 114.4; MS *m/z* $(M)^{+}$ calcd (without HCl) 153.1, obsd $(M+H)^{+}$ 154.1. *Anal.* Calcd for $C_7H_8ClNO_3$: C, 44.34; H, 4.25; N, 7.39; Cl, 18.70. Found: C, 44.13; H, 4.19; N, 7.43; Cl, 18.83.

3-Fluorenylmethoxycarbonylamino-5-hydroxybenzoic acid (2): 3-Amino-5-hydroxybenzoic acid hydrochloride **1** (114 g, 0.602 mol) was dissolved into saturated sodium bicarbonate (2 L) and the pH was adjusted to 8.2 by adding 5N NaOH dropwise. 9-Fluorenylmethyl chloroformate (156 g, 0.602 mol) was dissolved into THF (1 L) and added in one portion to the reaction mixture (observed pH goes immediately to 8.6 and then tapers off to 7.18 over a 3

minute period). Solid sodium bicarbonate (114 g) was added and the reaction was stirred for 4 days (the observed pH remained at 7.25). The insoluble solids were filtered off through celite, washed with saturated sodium bicarbonate, and the bulk of the THF was removed from the filtrate at 25°C/ 30 torr. The remaining solution was washed with heptane/ diethyl ether (2:1 ratio, 2 x 3L) and the organic layers were discarded. The pH of the aqueous phase was slowly adjusted to 1.5 using 6N HCl and then extracted with ethyl acetate (2 x 3L). The ethyl acetate extracts were combined and dried over $MgSO_4$ and charcoal. The solids were filtered off through celite and the filtrate was concentrated at 25°C/ 30 torr to give a white solid. It was necessary to dry this solid at 120°C/ 30 torr to remove ethyl acetate and give 165 g of 3-fluorenylmethoxycarbonylamino-5-hydroxybenzoic acid **2** in 74% yield. ^{1}H NMR (DMSO) δ 8.80 (bs, 2 H), 7.94 (d, J=7.0 Hz, 2 H), 7.78 (d, J=7.5 Hz, 2 H), 7.57 (s, 1 H), 7.45-7.30 (m, 4 H), 7.25 (s, 1 H), 6.99 (s, 1 H), 4.42 (d, J=7.0 Hz, 2 H), 4.30 (t, J=6.5 Hz, 1 H); ^{13}C NMR (DMSO) ppm 167.4, 157.9, 153.5, 143.9, 140.9, 132.4, 127.9, 127.3, 125.3, 120.3, 110.4, 109.5, 65.7, 46.6; MS *m/z* $(M)^+$ calcd (without HCl) 375.4, obsd $(M)^+$ 375.2. *Anal.* Calcd for $C_{22}H_{17}NO_5$: C, 70.39; H, 4.56; N, 3.37. Found: C, 70.35; H, 4.49; N, 3.55.

References:

1) a. Dankwardt, S.M., Phan, T.M., and Krstenansky, J.L., *Molecular Diversity*, 1 (**1995**) 113-120. b. Rickards, R. et. al., International Patent # WO 84/ 00750. "Process for the Preparation of 3-Amino-5-hydroxybenzoic acids and Derivatives and Analogues Thereof" (**1983**). c. Rickards, R.W., Becker, A.M. *Tetrahedron*, 39, (**1983**), 4189.

2) Cabel, D., personal communication with Flynn, G.A., Selectide Inc., a subsidiary of Hoechst Marion Roussel.

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