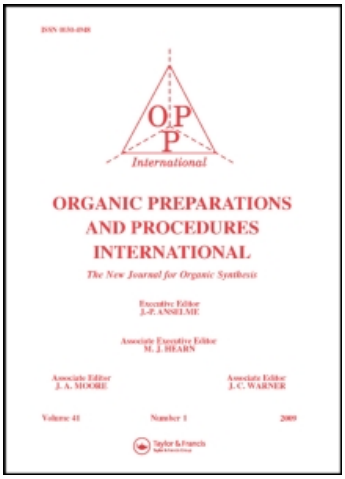

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SYNTHESIS OF 2-CHLORO-4-FLUORANILINE

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SYNTHESIS OF 2-CHLORO-4-FLUORANILINE

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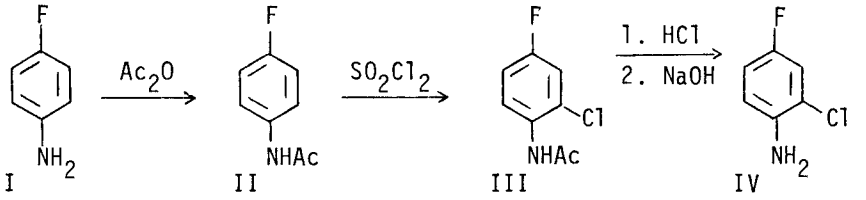
Literature procedures for the preparation of 2-chloro-4-fluoroaniline (IV) are either inconvenient or difficult to control or proceed in low yields.[1] We have developed a convenient, high yield synthesis of IV from I as shown in the equation. This synthesis can be scaled up to 2 mole quantities.



EXPERIMENTAL

4-Fluoroacetanilide (II). - 4-Fluoroaniline (I, 226.8 g, 2.04 mol) was cooled in an ice bath and treated dropwise with acetic anhydride (225 mL) over a period of 1 hr. The resultant paste was quenched with ice-water (1.5 L). The precipitate was collected, washed with water and dried in a vacuum oven over P_2O_5 at 80° for 4 hrs (prolonged drying caused some product loss as a result of sublimation in the oven). The tan product (298.5 g, 95%) melted 147.5-151°, lit.[1] mp 152°; and was used without further purification.

2-Chloro-4-fluoroacetanilide (III). - A solution of II (298.0 g., 1.95 mol) in chloroform (1.7 L) was treated dropwise with sulfuryl chloride (298 g.,

170 mL, 2.14 mol) and the mixture was refluxed overnight; the addition of sulfuryl chloride should be done with care because the reaction is exothermic. The solution was cooled, sulfuryl chloride (85 mL) was carefully added and the mixture was refluxed 4 hrs. The dark solution was cooled, concentrated and the residue was dissolved in 500 mL hot ethanol. The solution was treated with activated charcoal, filtered through diatomaceous earth and diluted with water (300 mL). Upon cooling, the first crop (190.3 g, 52%) of the tan solid was collected. Concentration of solvent to half volume resulted in the isolation of a second crop of product, 116.5 g (32%). Recrystallization from ethanol-water gave an analytical sample of III, mp 115-116°, lit.[1] mp 117°.

2-Chloro-4-fluoroaniline (IV). - Anilide III (299.24 g, 1.60 mol) was treated with 6N hydrochloric acid (1.5 L) and the mixture was refluxed for 1 hr and allowed to stand at room temperature overnight.[2] The reaction mixture was treated with 5N sodium hydroxide (2.0 L) and extracted with methylene chloride (4x). The combined organic layers were dried over sodium sulfate, concentrated and distilled to give 184.0 g (79%) of IV as a pale yellow liquid, bp 70-71°/0.25 mm Hg, 98-102° (aspirator), lit.[1] bp 192°/760 mm Hg.

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2. The resulting tan product (IV·HCl) could be isolated by filtration and stored indefinitely, mp 212-214°. Anal. Calcd for $C_6H_6ClFN\cdot HCl$: C, 39.59; H, 3.32; N, 7.70; Cl, 38.96; F, 10.44. Found: C, 39.70; H, 3.29; N, 7.85; CL 38.47; F, 10.56.