A new approach for the synthesis of 4-chloro-2-fluoronitrobenzene

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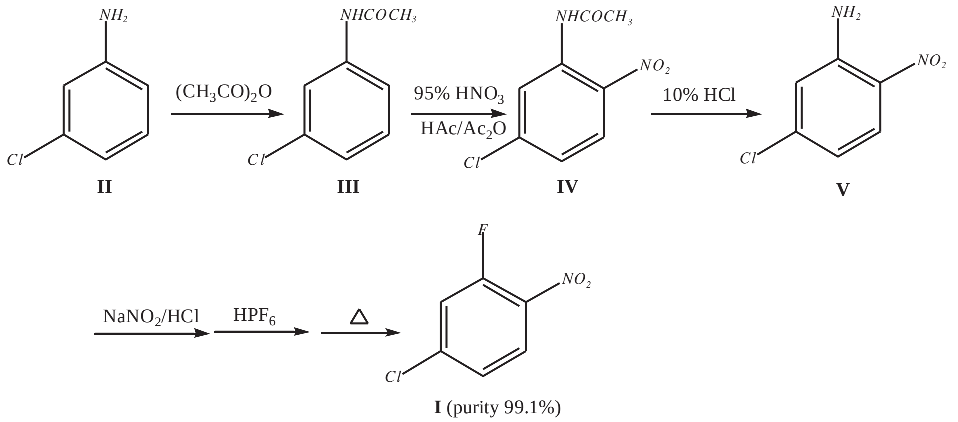
A new approach to the preparation of 4-chloro-2-fluoronitrobenzene in high purity is developed using 3-chloroaniline as a starting material, comprising acetylation, nitration, deprotection and a Schiemann reaction.

Keywords: 4-chloro-2-fluoronitrobenzene, 3-chloroaniline, synthesis



Scheme 1

4-Chloro-2-fluoronitrobenzene (**I**) is a useful intermediate[1] for pesticides and pharmaceuticals. Most efforts[2-4] have been made to prepare **I** with a halogen-exchange reaction using 2, 4-dichloronitrobenzene as a starting material, which reacted with KF in the presence of an aprotic polar solvent such as DMSO, DMF or sulfolane. However, the results were not satisfactory because the product from the reaction was a mixture of 2,4-difluoronitrobenzene, 2-chloro-4-fluoronitrobenzene, and **I**. The yield of **I** was poor, and the purification was difficult. Another disadvantage in these methods was the vigorous reaction conditions such as the high temperature (mostly 180–250°C) and the long reation time. Although the halogen-exchange reaction could be carried out at an enhanced reaction rate and at a lower temperature if certain quaternary ammonium complexes were present in the reaction mixture[5], the selectivity and yield of **I** were still quite low.

Another method to prepare **I** comprises the reacting of KF with 3,4-dinitrochlorobenzene in the presence of sulfonate and phthaloyl chloride.[6] The reported yield of **I** was up to 90%. However, the reactants 3,4-dinitrochlorobenzene and phthaloyl chloride are expensive. Additionally, the purity of 3,4-dinitrochlorobenzene available at present is only 90%, which may limit the purity of product **I**.

In our laboratory, an attempt to prepare **I** was made by nitration of *m*-chlorofluorobenzene, but the main product was 2-chloro-4-fluoronitrobenzene, an isomer of **I**. The selectivity to **I** was merely 20–30%.

A well-known alternative for introducing a fluoride to an aromatic ring is the Schiemann reaction, which involves the use of fluoroboric acid or its derivatives or hexafluorophosphoric acid for the conversion of aromatic amines into the corresponding fluorides. However, there is no report on the application of the Schiemann reaction to the preparation of **I**.

With this in mind, a new approach to the preparation of **I** was developed using 3-chloroaniline as a starting material, comprising acetylation, nitration, deprotection, and the Schiemann reaction (Scheme 1).

In order to increase the regioselectivity of the nitration of 3-chloroacetanilide (**III**), the conversion was controlled at about 30%, so that a selectivity of above 98% to 5-chloro-2-nitroacetanilide (**IV**) was obtained, which ensured a high purity of the **I** produced. The un-reacted **III** could be reused.

Although the diazotisation of **V** was not easily performed in dilute hydrochloric acid, it was readily completed in concentrated hydrochloric acid, owing to the increasing of solubility of **V** in the medium. (See **Caution** about diazonium salt in the Experimental section).

In conclusion, **I** was conveniently prepared with easily available and inexpensive reagents and under mild reaction conditions in high purity and good yield.

Experimental

Melting and boiling points are uncorrected. The purity of product was determined on a Fuli GC-9790 gas chromatograph with FID, SE-30 capillary column (3.2mm × 30 m). IR spectra were recorded on a Bruker EQUINOX 55 spectrometer. ^{1}H NMR spectra were determined on a Bruker AC-400 instrument. Chemical shifts are reported in ppm downfield from internal TMS. MS spectra were recorded on a Varian CP 3800/Saturn 2000 GC/MS. Elemental analyses were performed using a Heraus Carlo Erba 1108 analyser.

3-Chloroacetanilide **(III)** was prepared according to the known method[7]: acetic anhydride (69.0 g, 0.67 mol) was added dropwise to a stirred 3-chloroaniline (**II**, 50.0 g, 0.39 mol) suspended in 450 ml of water, warmed to 35–40°C, over a period of 40 minutes. After the addition, the reaction mixture was stirred at the same temperature for 4 h. After cooling to room temperature, the reaction mixture was filtered, and the product washed with water (100 ml × 3) and dried to give 60.8 g of **III** as a white solid. Yield 91.5%, m.p. 70–71°C (lit.[7] 72.5–73°C).

5-chloro-2-nitroacetanilide **(IV)**: 95% Fuming nitric acid (1.49 g/ml, 7.4 g, 0.10 mol) in 9 ml of acetic acid was added dropwise to a stirred solution of **III** (50.0 g, 0.29 mol) in 55 ml of acetic acid and 60 ml of acetic anhydride at –10 to –5°C. After completion of the addition, the reaction mixture was stirred for 1 h at 0 to 5°C and then decanted into ice water. The yellow solid was collected by filtration, stirred for

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30 minutes with water, filtered, and then stirred for 20 minutes with 150 ml of ether and filtered. Drying of the solid gave 11.0 g of **IV** as a light tan solid, purity 99.1%, m.p. 114–115˚C (lit.[7] 114–116˚C). The mother liquor was extracted with ether (100 ml×3). The extracts were combined and evaporated to dryness to recycle **III** (35.2 g), which could be reused.

5-chloro-2-nitroaniline **(V)**: A mixture of **IV** (32.0 g, 0.15 mol) suspended in 10% hydrogen chloride aqueous solution was stirred and refluxed for 2 hours. After cooling to room temperature, the reaction mixture was neutralized with sodium carbonate to pH 10. The product was filtered, washed with water and dried to provide **V** (25.3 g, yield 98.4%) as a golden solid. M.p. 128–129˚C (lit.[7] 124–126˚C).

4-chloro-2-fluoronitrobenzene **(I)**: Sodium nitrite (3.4 g, 49 mmol) in 10 ml of water was added dropwise to a stirred solution of **V** (8.0 g, 46 mmol) in 280 ml of concentrated hydrochlonic acid cooled at 5–10˚C, over a period of 60 minutes. After further stirring at the same temperature for 60 minutes, hexafluorophosphoric acid (40%, 33.8 g) was added and the obtained mixture was stirred at 0–5˚C for 2 hours. The precipitate was collected by filtration, washed sequentially with cold water, ethanol and ether and air dried to give a slightly yellow solid (12.4 g)

CAUTION: The dry diazonium salt is explosive under high temperature.

The dry diazonium salt was added in portions to dichlorobenzene at about 150˚C with stirring over a period of 20 minutes. Decomposition of the salt proceeded smoothly and the same temperature was maintained for a further 1 hour. After cooling to room temperature, the reaction mixture was poured into sodium carbonate solution and partitioned. The organic layer was washed with water, dried with anhydrous sodium sulfate and distilled at reduced pressure with a Vigreux column. The distillate of 133–136˚C/30 mmHg was collected to give **I** (4.1 g, yield 50.3%, purity 99.1% by area normalisation) as a colourless liquid, which solidifies at room temperature. M.p. 46–48˚C (lit.[8] 48–49˚C). IR(KBr): 3103, 1605, 1564, 1523, 1343, 911, 860, 830, 748 cm^{-1}. MS (*m/e*): 175 (M$^+$), 145 (M$^+$-NO), 129 (M$^+$-NO$_2$), 109 (129-HF), 93 (129-HCl), 74 (93-F). ^{1}H-NMR (CDCl$_3$): δ 8.05 (1H, dd, *J* = 8.7, 8.2), 7.34–7.26 (2H, m). *Anal.* Calcd for $C_6H_3ClFNO_2$: C, 41.05; H, 1.72; N, 7.98. Found: C, 41.11; H, 1.74; N, 7.92.

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