A new approach to the synthesis of 2,6-dichloro-3-fluorobenzonitrile: a useful pharmaceutical intermediate

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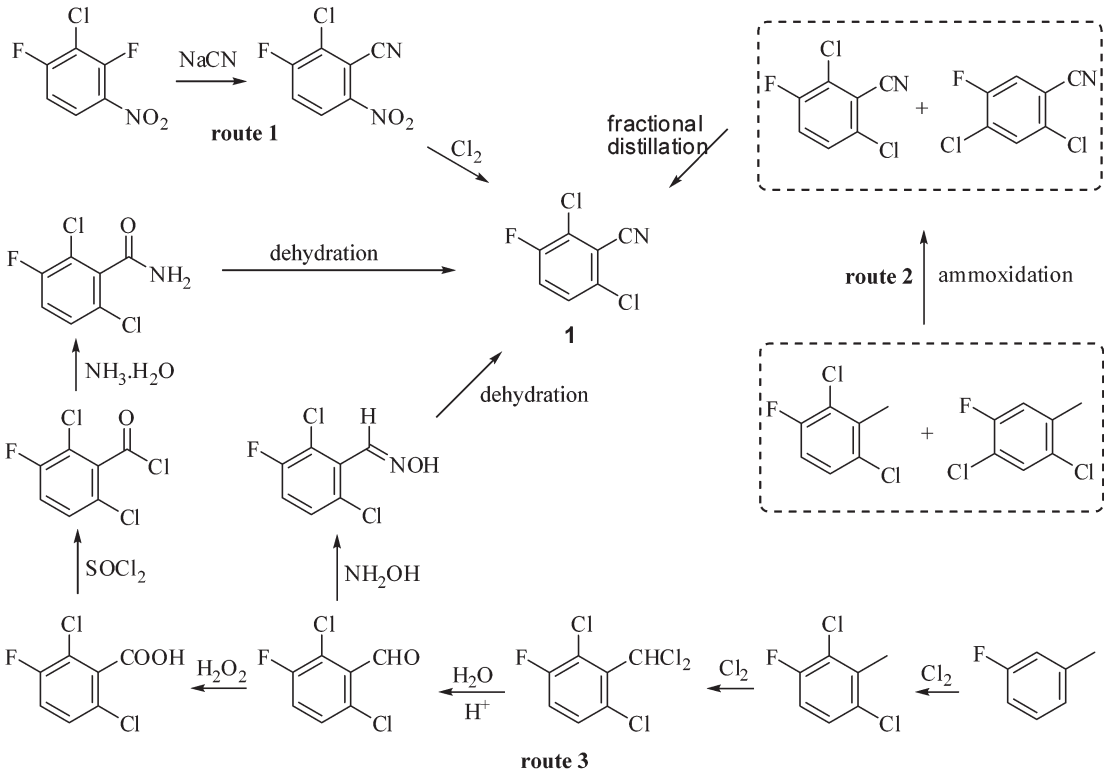
A highly efficient manufacturing-scale process for the preparation of 2,6-dichloro-3-fluorobenzonitrile, utilising industrial by-product 2,6-dichloro-3-fluoroacetophenone as starting material, has been developed. The overall yield was 77%.

Keywords: 2,6-dichloro-3-fluoroacetophenone, 2,6-dichloro-3-fluorobenzonitrile, synthesis

2,6-Dichloro-3-fluorobenzonitrile **1** is a useful intermediate in the synthesis of pharmaceuticals and plant protection agents.[1] Itaru *et al.*[2] reported a synthesis from 3-chloro-2,4-difluoronitrobenzene in which the fluorine atom at position 2 was replaced with cyanide to give 2-chloro-3-fluoro-6-nitrobenzonitrile and converted by chlorolysis of the nitro group into compound **1** (Scheme 1, route 1). Hagedorn *et al.*[1] described a process in which an isomeric mixture of 2, 4-dichloro-5-fluorotoluene and 2,6-dichloro-3-fluorotoluene was subjected to ammoxidation with ammonia, air and steam in the gas phase at a temperature of 550°C. The resultant formed mixture of 2,4-dichloro-5-fluorobenzonitrile and 2,6-dichloro-3-fluorobenzonitrile was separated by reduced pressure fractional distillation to give product **1** (Scheme 1, route 2). Lantzsch *et al.*[3] indicated that the target molecule could be prepared from 1-fluoro-3-methylbenzene via a five or seven-step synthetic route (Scheme 1, route 3). Most of these methods have their own merits. However, each suffered either from employing expensive catalyst, low yield, or especially high temperature and high material pollution of the equipment which was used thus limiting their industrial applications.

In the production of 2,4-dichloro-5-fluoroacetophenone, a key intermediate for the preparation of the fluoroquinolone antimicrobial agents,[4] 2,6-dichloro-3-fluoro acetophenone **2** is unavoidably generated as a by-product.[5] This isomeric by-product exists in the form of a mixture called "crystallisation mother liquor" mainly containing these two isomers, obtained in the purification stage. Since there were no efficient and economical ways to separate these two isomers because of the tiny differences of physicochemical properties, this "crystallisation mother liquor" was treated as industrial waste and burned. This not only raised air pollution, but also wasted resources. In our previous work[6], the isomers were successfully separated chemically (Scheme 2), utilising a difference in the reactivity of the carbonyl groups due to the steric hindrance.

As part of our interest in developing the uses for this "crystallisation mother liquor", we now report a highly efficient and convenient method for the preparation of **1** utilising a starting material isolated from this industrial by-product. The synthetic route is shown in Scheme 3.



Scheme 1

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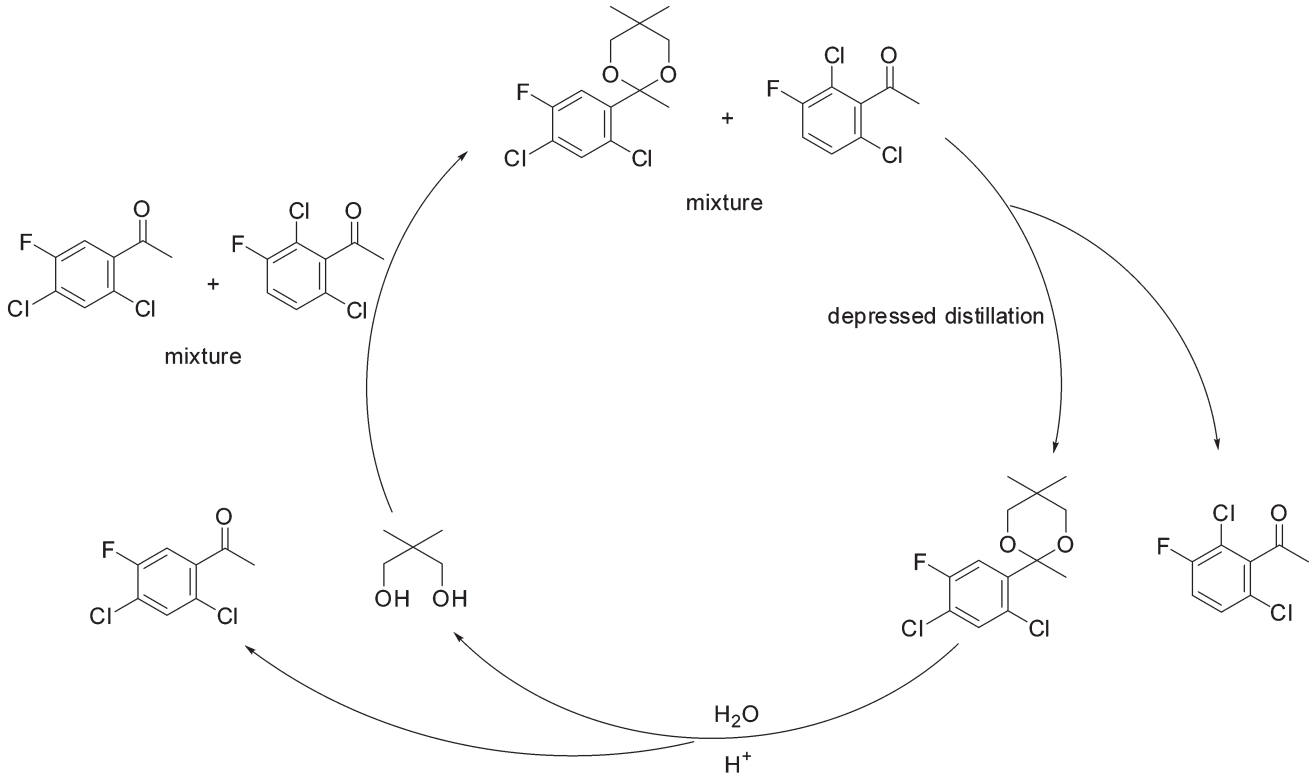
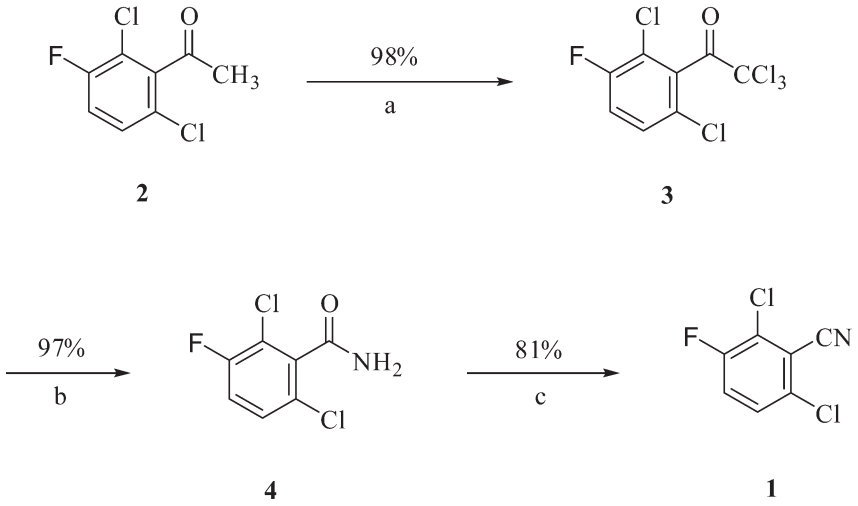


Scheme 2



a) Cl_2, NaOAc; b) NH_3; c) BTC/DMF

Scheme 3

A conventional way for the synthesis of compound **4** could be achieved by oxidation of **2** to a benzoic acid by an oxidant, followed by halogenation and then ammonolysis. Unfortunately, the oxidation reaction of **2** yielded the corresponding benzoic acid in a very low yield (< 30% at best) due to lack of selectivity, when $KMnO_4$ was used as the oxidant. Though the haloform reaction is effective in oxidative degradations of methyl ketones to carboxylic acids,[7,8] strongly basic conditions are required, accompanied by a large quantity of waste water. As a modification and simplification for preparation of **4**, we have adopted a method that involved of tri-chlorination at the methyl group of **2**, and ammonolysis of the resultant compound **3**. Satisfyingly, **3** was obtained in nearly quantitative yield (98%) by treating **2** with chlorine gas in a NaOAc/AcOH system. Moreover, **3** was smoothly transformed in good yield (97%) into **4** by ammonolysis with ammonia gas in ethanol which was used as a suitable green solvent.

A conventional dehydration reaction employs toxic reagents such as $POCl_3$ and $SOCl_2$ that are harmful to human health and hazardous to the environment.[9] Previously, we reviewed *bis*-(trichloromethyl) carbonate (BTC) as a mild, safe, easily handled, highly efficient and environmentally benign reagent.[10] It is convenient for use as a substitute for traditional reagents such as $POCl_3$, $SOCl_2$, phosgene, trichloromethyl chloroformate

(TCF, diphosgene). Here, BTC was employed as a dehydrating reagent with DMF as a catalyst in the conversion of **4** to **1**. After optimisation of the solvent, temperature and catalyst mole ratio, the reaction was carried out in EtOAc between 60°C and reflux with 20 mol% DMF, to afford **1** in a yield of 81%.

In conclusion, a highly efficient new approach to the synthesis of 2,6-dichloro-3-fluorobenzonitrile has been developed. The attractive features of this protocol are simple reaction procedure, high yield, and mild reaction conditions. As a highlight, an industrial by-product is utilised as the starting material, making this production method economically advantageous and beneficial for environment- protection.

Experimental

^{1}H NMR and ^{13}C NMR spectra were measured on a Varian 400 (400 MHz) spectrometer (chemical shifts in δ ppm) using TMS as internal standard. Mass spectra (EI-MS) were determined on a Thermo Finnigan LCQ-Advantage. Melting points were measured on a Büchi B-540 capillary melting point apparatus.

Synthesis of α,α,α,2,6-pentachloro-3-fluoroacetophenone (**3**): Chlorine gas was slowly bubbled into a solution of **2** (82.8 g, 400.0 mmol) in AcOH (250 mL) in a flask equipped with a condenser while stirring at 60°C for 5 h. The products were 2,6,α-trichloro-3-fluoroacetophenone and 2,6,α,α-tetrachloro-3-fluoroacetophenone with a mole ratio of approximately 2:1. NaOAc (65.6 g, 800.0 mmol) was added, the temperature was raised to 100°C and the chlorine gas was passed in for a further 1h. Excess chlorine was swept out with nitrogen, the mixture was cooled, and NaCl formed in the reaction was filtered. After removal of the solvent AcOH, the residue was dissolved in EtOAc (250 mL), washed with water, dried over Na_2SO_4 and concentrated in vacuo to give intermediate compound **3** as light yellow oil (121.7 g, 98%).

Synthesis of 2,6-dichloro-3-fluorobenzamide (**4**): **3** (121.7 g, 391.9 mmol) was dissolved in ethanol (600 mL). The gas from liquid ammonia was then slowly bubbled into the solution until it was saturated while controlling the temperature below 20°C with vigorous stirring. After completion of the reaction, the final solution was evaporated under reduced pressure to give crude compound **4** as light yellow solid (79.1 g, 97%). m.p. 181–185°C (183–186°C[3]). ^{1}H NMR (DMSO-d_6) δ: 7.50(t, *J* = 8.8 Hz, 1H), 7.56 (dd, *J* = 4.8, 8.8 Hz, 1H), 7.88–8.02 (brs, 1H), 8.08–8.24 (brs, 1H). ^{13}C NMR (DMSO-d_6) δ: 117.3 (d, *J* = 22 Hz), 118.0 (d, *J* = 20 Hz), 125.7, 129.5, 129.6, 138.7, 156.2 (d, *J* = 247 Hz), 164.3. EI-MS (*m/z*, %): 207 (M^+, 35), 191(100), 163(42), 128(19), 93(16), 74(6).

Synthesis of 2,6-dichloro-3-fluorobenzonitrile (**1**): Compound **4** (79.1 g, 380.3 mmol), BTC (48.9 g 164.8 mmol), and DMF (5.6 g, 76 mmol) were added to EtOAc (250 mL). The temperature was raised to 60°C, and after completion of the reaction, the reaction mixture was cooled to r.t. and washed with water until it was neutral. The solution was then dried over Na_2SO_4 and evaporated under reduced pressure to give crude product **1**. Further purification by vacuum distillation at 130°C/20 mmHg yielded **1** as white solid (58.5 g, 81%). m.p. 74–75°C (70–72°C[3]). ^{1}H NMR ($CDCl_3$) δ: 7.39(t, *J* = 8.8 Hz, 1H), 7.45 (dd, *J* = 4.4, 8.8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 112.4 (d, *J* = 2 Hz), 115.7, 121.5 (d, *J* = 22 Hz), 125.8 (d, *J* = 21 Hz), 129.2 (d, *J* = 7 Hz), 133.4 (d, *J* = 4 Hz), 156.9 (d, *J* = 251 Hz). EI-MS (*m/z*, %): 189 (M^+, 100), 154(39), 118(13), 99(8).

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