A novel and facile method for synthesis of 2,4-dichloro-3-cyano-5-fluorobenzoic acid

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A two-step facile process for the preparation of 2,4-dichloro-3-cyano-5-fluorobenzoic acid, starting from easily available 2,6-dichloro-3-fluorobenzonitrile, has been developed. The overall yield was 58%.

Keywords: 2,4-dichloro-3-cyano-5-fluorobenzoic acid, 2,6-dichloro-3-fluorobenzonitrile, synthesis

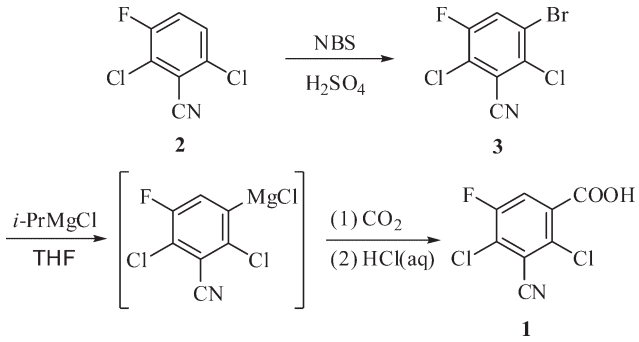
2,4-Dichloro-3-cyano-5-fluorobenzoic acid is the key intermediate for synthesis of finafloxacin hydrochloride (BAY35-3377), a novel fluoroquinolone antibiotic that is currently in clinical trial.[1] M. Schriewer *et al.* reported a synthetic method from a 2,4-dichloro-5-fluorobenzoic acid that involved nitration, reduction, diazotisation and a Sandmeyer reaction to give final product **1** (Scheme 1, route 1).[2] The main disadvantage of this process is, in particular, the Sandmeyer reaction, which proceeds with poorly reproducible yield and employs three extra equivalents of cyanide thus resulting in considerable hazard potential. The objective compound **1** was also prepared by Marhold and Wolfrum[3] from 5-fluoro-1,3-xylene, via a five-step synthetic route (Scheme 2, route 2). But it also suffered from disadvantages of low overall yield (less than 30%) and complicated manipulations.

Recently, we reported a highly efficient new approach to the synthesis of 2,6-dichloro-3-fluorobenzonitrile **2**, an important intermediate used in the synthesis of pharmaceuticals and plant protection agents.[4] As part of our attempt focused on developments of pharmaceutical intermediates, we now report a novel and facile method for preparing **1** starting from this commercially available material, as shown in Scheme 2.

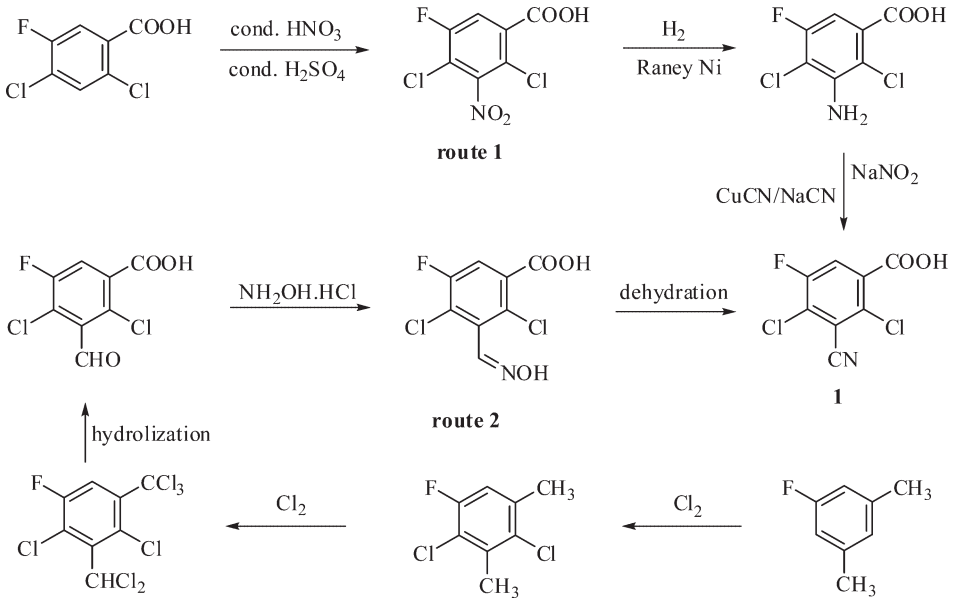
Results and discussion

For bromination of **2**, a series of methods were investigated. Compound **2** failed to be brominated by the common brominating agent Br_2 in the presence of Lewis acids or protonic acids, owing to the weakly electrophilic benzene nucleus of **2** (Table 1, entries 1–4). $KBrO_3$ was successful in carrying out bromination of **2** in the presence of a strong acid *e.g.* sulfuric acid (Table 1, entry 6), but unfortunately the yield was not satisfactory, as the reaction was accompanied by a considerable amount of by-product due to the strong oxidisability of $KBrO_3$. But by employing NBS as brominating agent in concentrated sulfuric acid[5] (Table 1, entry 8), **2** was smoothly brominated into 2,6-dichloro-3-fluoro-5-bromobenzonitrile **3** in high yield (97%).

The preparation of polyfunctional organometallics has long been an active research field, especially the functionalised Grignard reagents which are key organometallics in organic synthesis. Recently, Knochel's group reported an interesting



Scheme 2



Scheme 1

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Table 1 Bromination of 2,6-dichloro-3-fluorobenzonitrile

Entry	Brominating agent	Solvent	Catalyst	Temperature /°C	Reaction time /h	Yield /%
1	Br_2	$ClCH_2CH_2Cl$	$AlCl_3$	Reflux	24	NA
2	Br_2	$ClCH_2CH_2Cl$	$FeCl_3$	Reflux	24	NA
3	Br_2	$ClCH_2CH_2Cl$	Fe	Reflux	24	NA
4	Br_2	AcOH	H_2SO_4	Reflux	24	NA
5	$KBrO_3$	AcOH	/	Reflux	24	NA
6	$KBrO_3$	AcOH/H_2SO_4[a]	/	r.t.	30	42[b]
7	NBS	F_3CCO_2H	/	Reflux	24	NA
8	NBS	H_2SO_4	/	r.t.	36	97

[a] Vol/vol 7:3.
[b] The best yield at optimised condition.

method for preparation of functionalised Grignard reagents by the direct insertion of magnesium in the presence of LiCl.[6] But since the cyano group in substrate **3** was highly sensitive, applying this method to compound **3** failed badly as reduction and coupling products formed as the main products, accompanied by large amount of products from reaction of the cyano group with the highly reactive magnesium intermediate.

Other methods for preparing polyfunctional Grignard reagents includes I/Mg exchange and Br/Mg exchange reactions.[7–10] Since aryl and heteroaryl bromides are cheaper and more readily available as starting materials, they are more commonly used as the substrates. Thus **3** was treated with *i*-PrMgCl, a commercially available reagent that could be efficiently used to carry out Br/Mg exchange, and 2,6-dichloro-3-fluoro-5-bromo-benzyl-magnesium reagent was successfully generated. This Grignard reagent was further subjected to carboxylation with CO_2, followed by acidification to afford target compound **1** with a yield of 60%.

In conclusion, a two-step and efficient novel approach to the synthesis of 2,4-dichloro-3-cyano-5-fluorobenzoic acid, which could be extended to large-scale production, was developed. The attractive features of this protocol are simple reaction procedure, high overall yield and avoiding employing highly toxic reagents.

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 were determined on a Thermo Finnigan LCQ-Advantage. Melting points were measured on a Büchi B-540 capillary melting point apparatus.

2,6-Dichloro-3-fluoro-5-bromobenzonitrile (**3**): **2** (19.0 g, 100.0 mmol) and NBS (21.4 g, 120.0 mmol) were dissolved in concentrated sulfuric acid (50.0 mL), and stirred at r.t. for 36 h. The reaction mixture was then poured into ice-water and stirred for 15 min. The resulting milky-white solid was filtered, washed with H_2O and dried, giving **3** as a white powder (26.1 g, 97%), m.p. 122–124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.1 (d, J = 3 Hz), 116.5, 122.1 (d, J = 9 Hz), 125.1 (d, J = 20 Hz), 125.2 (d, J = 24 Hz), 134.0 (d, J = 4 Hz), 156.0 (d, J = 254 Hz). EI-MS (*m/z*, %): 269 (M^+, 100), 188 (24), 153 (16). EI-HRMS: *m/z* (M^+) Calcd for C_7HBrCl_2FN: 266.8653; found: 266.8672.

2,4-Dichloro-3-cyano-5-fluorobenzoic acid (**1**): *i*-PrMgCl (116.5 mL, 116.5 mmol, 1 M in THF) was cooled to –50 °C and to this solution was slowly added **3** (26.1 g, 97.1 mmol) with vigorous stirring, while maintaining this temperature. The Br/Mg exchange reaction was complete after 1 h, and dry CO_2 was then slowly bubbled in for a further 1 h with the temperature being raised to –5 °C. After acidification by aqueous HCl solution (1 M), THF was evaporated, and the aqueous phase was extracted with EtOAc, dried over Na_2SO_4, and concentrated *in vacuo*. Further purification by recrystallisation from toluene yielded pure product **1** as light yellow crystals (13.6 g, 60%). m.p. 204–206 °C (lit.[2] 203–205 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (d, J = 9.2 Hz, 1 H), 14.23 (brs, 1 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 112.8 (d, J = 3 Hz), 116.1, 122.5 (d, J = 24 Hz), 126.6 (d, J = 21 Hz), 130.7 (d, J = 3 Hz), 134.1 (d, J = 6 Hz), 155.7 (d, J = 248 Hz), 163.9. ESI-MS (*m/z*, %): 233 ([M-H]$^-$, 100), 189 (30).

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