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A New Synthetic Route for Preparation of 2-Chloro-6-fluoro-benzonitrile and 2-Chloro-6-fluorobenzoic Acid

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Abstract: An effective synthetic route for preparation of 2-chloro-6-fluorobenzonitrile, 2-chloro-6-fluorobenzamide and 2-chloro-6-fluorobenzoic acid has been described. It includes diazotization, fluorination, ammoxidation and hydrolysis reactions.

Keywords: 2-Chloro-6-fluorobenzonitrile, 2-chloro-6-fluorobenzamide, 2-chloro-6-fluorobenzoic acid, ammoxidation, hydrolysis.

2-Chloro-6-fluorobenzonitrile, 2-chloro-6-fluorobenzamide and 2-chloro-6-fluoro- benzoic acid are key intermediates for synthesizing many pharmaceuticals and agro-chemicals, such as benzylphenyltriazole, benzylphenyloxazole and benzamidoximes derivative[1-4]. Quinazoline analogues of folic acid used as potential chemotherapeutic agents from 2-chloro-6-fluorobenzonitrile can be obtained in higher yield than other synthetic methods[5-6]. 2-Chloro-6-fluorobenzamide is also widely used in synthesis of benzoylphenyl ureas[7].

So far, three methods have been reported for the synthesis of 2-chloro-6-fluorobenzonitrile. J. H. Clark *et al.* synthesized 2-chloro-6-fluorobenzonitrile by treating 2-chloro-6-nitrobenzonitrile and KF *via* halogen transfer reaction[8]. Because the starting material is expensive, this method could be used only in laboratory. Chempolil Thomas Mathew *et al.* synthesized 2-chloro-6-fluorobenzonitrile from 2-chloro-6-fluorobenzaldehyde *via* aldoxime dehydration[9]. But the disadvantages of the expensive starting material and serious pollution problems still exist. Mark W. Zettler *et al.* obtained 2-chloro-6-fluorobenzonitrile as an intermediate during the synthesis of 2, 6-difluorobenzonitrile from 2,6-dichlorobenzonitrile[10]. Because of difficulty in separating 2-chloro-6-fluorobenzonitrile from 2,6-difluorobenzonitrile, this method could not be used in practice.

In the previous paper[11], 2-chloro-6-fluorobenzoic acid had been synthesized by oxidizing 2-chloro-6-fluorobenzaldehyde. Not only the starting reagent is expensive, but also the yield is poor.

The new route for preparation of 2-chloro-6-fluorobenzonitrile, 2-chloro-6-

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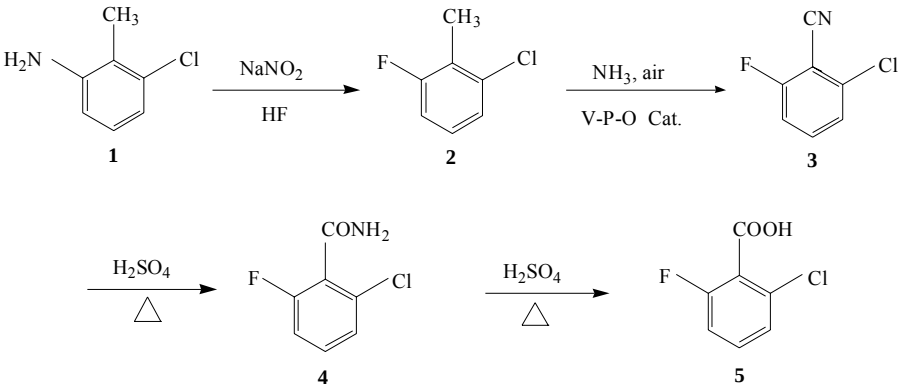
fluorobenzamide and 2-chloro-6-fluorobenzoic acid is shown as **Scheme 1**. The first step of this synthesis is diazotization and fluorination from cheap starting material 3-chloro-2-methylbenzenamine **1**. In the second step, 2-chloro-6-fluorotoluene **2** is converted into corresponding nitrile by catalystic ammoxidation under suitable conditions, which needs only one step without pollution. Usually, the two groups in the ortho-position of the ring would inhibit the hydrolysis of nitrile to amide and acid. However, we have found the optimal hydrolysis reaction conditions and obtained amide and acid from nitrile with high yields.

Scheme 1 the new synthetic route using ammoxidation



Experimental

Products were characterized by ^{1}HNMR and IR spectra. The ^{1}HNMR spectrum was recorded on an OXFORD NMR AS 300 spectrometer with TMS as an internal standard. The IR spectrum was recorded on an AVATAR 380 infrared spectrophotometer. The melting point was determined with a X6 microscopic warming apparatus and the thermometer was not calibrated. The purity of products was tested with SP-502 gas chromatograph.

*Preparation of 2-chloro-6-fluorotoluene **2***

85 g (0.60 mol) **1** and 60 g anhydrous hydrogen fluoride was mixed in a stainless steel reactor. 43.5 g dry $NaNO_2$ was added in portions at 0~5°C. After that the reactor system was stirred for half an hour. Then the temperature was risen and the resulting diazonium fluoride was decomposed at 80°C. The resulting solution was neutralized with concentrated ammonia water, the oil layer was separated, washed and **2** was obtained by vapor distillation in 85 % yield. b.p. 154~156°C. The purity was above 99 % by GC. IR (KBr, cm^{-1}): 3051(w), 2938(m), 2862(w), 1615(s), 1587(s), 1470(s), 1379(m). ^{1}HNMR ($CDCl_3$, δppm): 2.25-2.40(d, 3H, C**H**$_3$,$J_{F\text{-}CH3}$=2.3Hz), 6.69-7.20(m, 3H, arom).

*Preparation of the catalyst used in the ammoxidation of **2***

$H_2C_2O_4 \cdot 2H_2O$ (3.67 g) was dissolved in 25 mL hot water. V_2O_5 (0.88 g), 85 % H_3PO_4 (1.12 g), CrO_3 (0.49 g), H_3BO_3 (0.12 g) and $TiCl_4$ (0.33 mL, 2.92 mol/L) were added, then 10 g SiO_2 (diameter 0.3~0.425 mm) was impregnated into the solution. After drying overnight, the catalyst was heated at 280°C for 2 h and calcined at 500°C for 5 h. The composition of the catalyst is $V_1P_1Cr_{0.5}B_{0.2}Ti_{0.1}O_{6.25}/SiO_2$.

Preparation of 2-chloro-6-fluorobenzonitrile 3 by ammoxidation

Based on our work[12], the experiment was carried out in a 30 mm-inside-diameter quartz tube fixed-bed reactor loaded 10 g above catalyst. **2** was vaporized, then mixed with air and NH_3. The mixed gas was preheated, and then passed through the reactor. The reaction temperature was controlled at 380±1°C by an AI-808 temperature adjuster. **2** was entered 0.5 mL per hour by a micropump. The molar ratio of air/**2** and NH_3/**2** were 25 and 6, respectively. After reaction, the product was cooled and condensed in a condensing apparatus. White solid was obtained after filtration and drying under vacuum. The reaction can be carried out continuously. The condensing apparatus was altered every 8 hours. The test lasted near 240 hours. 0.454 g nitrile **3** per 8 hr was obtained, molar yield 71.47 %. m.p. 56~59°C. The purity was above 99% by GC. IR (KBr, cm^{-1}): 3098(m), 2235(s), 1601(s), 1577(s), 1460(s). ^{1}HNMR ($CDCl_3$, δppm): 7.00-7.81(m, 3H, arom).

*Preparation of 2-chloro-6-fluorobenzamide **4***

A mixture of 3.89 g (0.025 mol) **3** and 30 mL 90 % H_2SO_4 was stirred in 100 mL three-necked flask at 90°C for 2 hours, then suspended in 150 mL water to obtain precipitate. After filtration, the white powder was recrystallized from ether to obtain colorless needle crystal (4.30 g, yield 98.9 %). m.p. 141~143°C. The purity was above 99 % by GC. IR (KBr, cm^{-1}): 3371(s), 3186(s), 1658(s), 1606(s), 1572(m), 1450(s), 1243(s). ^{1}HNMR ($CDCl_3$, δppm): 5.87-6.18(d, 2H,CON**H**$_2$), 7.04-7.38(m, 3H, arom)..

*Preparation of 2-chloro-6-fluorobenzoic acid **5***

A mixture of 1.74 g (0.010 mol) **4** and 30 mL 70 % H_2SO_4 was stirred in 100 mL three-necked flask at 140°C for 5 hours, then suspended in 150 mL water and resulting precipitate was filtrated off. Recrystallizing from diluted EtOH afforded 1.63 g (93.3 %) of white crystal **5**. m.p. 159~161°C. The purity was above 99 % by GC. IR (KBr, cm^{-1}): 3200(m, b), 3082(m), 1705(s), 1603(s), 1579(m), 1457(s), 1403(m), 1302(s). ^{1}HNMR ($CDCl_3$, δppm): 7.00-7.70(m, 3H, arom), 13.40(s, 1H,COO**H**).

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