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A Facile Two-Step Synthesis of 3-Fluoro-6-methoxyquinoline

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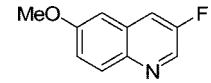
Abstract:

A facile two-step synthesis of 3-fluoro-6-methoxyquinoline is described. *p*-Anisidine was heated at reflux with 2-fluoromalonic acid in the presence of phosphorus oxychloride to produce 2,4-dichloro-3-fluoro-6-methoxyquinoline. This was followed by hydrogenolysis to produce 3-fluoro-6-methoxyquinoline.

Introduction

As an important class of alkaloids, quinoline compounds are of pharmaceutical interest due to their wide range of biological activities.[1] Several examples in the medicinal chemistry literature have demonstrated that fluorinated quinolines display improved performance relative to that of their des-fluoro analogues, which has resulted in the development of new pharmaceutical candidates incorporating fluoroquinolines.[2] We recently engaged in a program to develop a method for the preparation of 6-methoxy-3-fluoroquinoline (**1**, Figure 1). This communication describes the kilogram-scale synthesis of **1**.

The Schiemann reaction (fluorination of anilines with $NOBF_4$; see steps 6/7 in Scheme 1) remains one of the most common methods to introduce fluorines into heteroaromatic compounds.[3] When we engaged in this project, the only known preparation of **1** in the literature was a seven-step synthesis (Scheme 1)[4] that employed a Schiemann reaction in the final step. The chemistry was not deemed suitable for scale-up because of efficiency issues and some high-energy transformations (steps 2 and 6/7). We considered several alternative methods for the fluorination of quinolines. The method of



1

Figure 1

Schlosser et al.,[5] in which an aniline is condensed with methyl 2-fluoro-3-methoxyacrylate, required cryogenic conditions and the use of gaseous dichlorofluoromethane. Alternatively, Michael addition of *N*-tosylanilines to acrolein, followed by cyclization and thermal elimination, provides a convenient synthesis of quinolines.[6] Unfortunately, this method could not be adapted for the 3-fluoroquinoline synthesis as the requisite starting material, 2-fluoroacrolein, polymerized rapidly even under cold storage.

We considered the functionalization of chloroquinolines. Heteroaromatic chlorides are efficient ortho-metalation directing groups and readily removed via catalytic hydrogenolysis.[7] With this in mind, we initially embarked on the directed ortho-lithiation[8] of chloroquinolines **2a** and **2b**[9](Scheme 2), followed by addition of $(PhSO_2)_2NF$ as an electrophile. Unfortunately, this approach did not produce a meaningful yield of the desired 3-fluorinated products (**3**).[10]

In parallel to these lithiation studies, we investigated the synthesis of 2,4-dichloro-3-fluoroquinolines (**3b**) via an annulation approach, (Scheme 3). Analogous to the well-precedented synthesis of 2,4-dichloroquinoline,[11] *p*-anisidine was heated at reflux with 2-fluoromalonyl chloride, which was generated *in situ* by treating 2-fluoromalonic acid (**4**)[12] with phosphorus oxychloride. This process proved to be successful, and dichlorofluoroquinoline **3b** was obtained in ~60% yield. Removal

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(10) Trace amount of the desired product (<5%) was observed by LC/MS. The starting materials mostly decomposed. The investigation of this approach was limited to reaction conditions of LDA or LiTMP at −60 °C, then $(PhSO_2)_2NF$ addition.
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(12) Prepared from the commercially available dimethyl 2-fluoromalonate.

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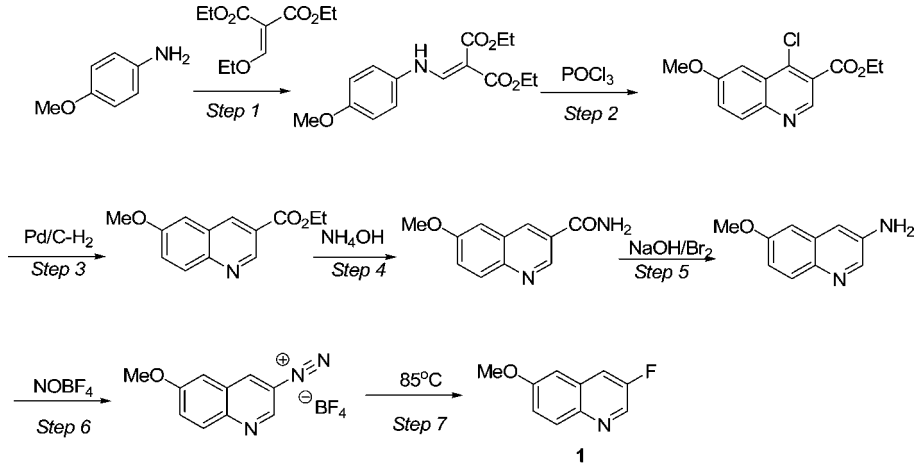
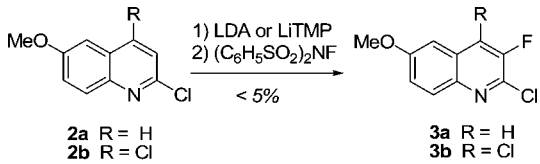
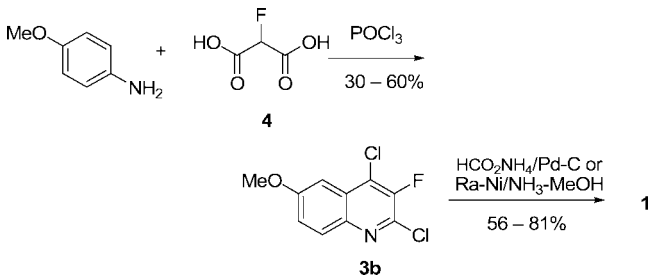
Scheme 1



Scheme 2



Scheme 3



of the chlorine by transfer hydrogenolysis or Raney nickel provided **1** in good yields. This protocol was subsequently executed on more than one kilogram scale.[13]

While 2-fluoromalonic acid derivatives are known to react with amidines, ureas, or guanidines to produce 5-fluorouracils or other pyrimidines,[14] their applications in Friedel−Crafts acylation/cyclocondensation reactions have not been documented in the literature. The findings reported herein demonstrate a new approach to the syntheses of 3-fluoroquinolines. This method may be amenable for syntheses of other compounds possessing the 3-fluoropyridine fragment.

Experimental Section

2-Fluoromalonic Acid (4). To dimethyl 2-fluoromalonate (45 g, 0.3 mol, LR) was added methanol (675 mL), water (45 mL), and lithium hydroxide (15.3 g, 0.63 mol). The mixture was stirred at room temperature for 16 h. The reaction was monitored with TLC (10% EtOAc/hexanes, I_2 visualization). The reaction suspension was stripped to ~135 mL. Water (67.5 mL) and MTBE (450 mL) were added. After cooling to 0 °C, concentrated HCl (66 mL, 37%, 0.66 mol) was added. The organic layer was separated, and the aqueous layer was extracted with MTBE (3 × 225 mL). The organic layers were combined, dried with sodium sulfate, and concentrated to give the product as a white solid (36.1 g, 99%). ^{1}H NMR (400 mHz, $CDCl_3$) δ (ppm) 5.4 (d, J = 2.1 Hz, 1H), 5.31 (d, J = 2.1, 1H), 5.15 (br, 4H). MS m/z $(M - H)^+$ 120.88.

2,4-Dichloro-3-fluoro-6-methoxyquinoline (3b). *Laboratory Scale.* To phosphorus oxychloride (210 mL) was added fluoromalonic acid (35 g, 0.287 mol, portionwise. The mixture was heated at reflux for 30 min to completely dissolve fluoromalonic acid and then cooled to 60 °C. After *p*-anisidine (35.3 g, 0.287 mol) was added slowly, the mixture was heated at reflux for 2 h, and then ~100 mL of phosphorus oxychloride was removed by distillation. The resulting mixture was cooled to RT and poured onto ice (350 g) and stirred for 30 min. Ammonium hydroxide (300 mL, 28−30%) was added to adjust the pH to 10. The suspension was stirred for 2 h before it was filtered. The filter cake was washed with water. After drying, the solid was regranulated in MTBE (200 mL) for 2 h. An off-white solid was collected and dried under vacuum at 45 °C to produce the first crop product (12.4 g). The filtrate was concentrated and exchanged with ethyl acetate to a volume of ~150 mL. Hexanes (150 mL) were added. The suspension was granulated for 2 h. Filtration of the slurry and drying under full vacuum gave the second crop product (19.6 g). The filtrate was chromatographed, eluting with 5% ethyl acetate in hexanes to produce additional product as the third crop (10.2 g). The combined crops were 42.2 g, 60% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 9.1 Hz, 1H), 7.38 (dd, J = 9.1, 2.9 Hz, 1H), 7.32 (d, J = 2.9 Hz, 1H), 3.98 (s, 3H). MS m/z 246.1 $(M + H)^+$; HRMS m/z Calcd for $C_{10}H_7NOFCl_2(M + H)^+$ 245.9889, Found: 245.9889.

Kilo Laboratory Scale. To phosphorus oxychloride (7.0 L) in a 12 L glass reactor equipped with a mechanical stirrer, condenser, and thermometer was added fluoromalonic acid (1109 g, 9.09 mol) portionwise. The mixture was heated at reflux for 30 min to completely dissolve fluoromalonic acid

(13) More robust isolation methods for both the intermediate **3b** and the final product will need to be explored for multikilogram-scale reactions.

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and then cooled to 60 °C. *p*-Anisidine (1119 g, 9.09 mol) was added over a period of 1.5 h at 60−65 °C (Caution: with each addition, there was a short duration of a rapid release of HCl gas and a minor exotherm). The mixture was heated to reflux (HCl gas continued to evolve during the heat-up; the reaction should be heated up slowly). Once the reaction temperature was >90 °C, the heating was continued for 2 h. (The final reaction temperature will be 100−105 °C). $POCl_3$ (1.5 L) was then removed by vacuum distillation. The resulting mixture was cooled to RT and slowly transferred into a 30 gal PE jug (equipped with an agitator) that contained ice (35 kg); the mixture stirred for 30 min. Ammonium hydroxide (30 L, 28−30%) was added to adjust the pH to 9.5−10 range. The suspension was stirred for 2 h before it was filtered. The filter cake was washed with water. The wet solids (3.2 kg) were transferred to the reactor, and EtOAc (9 L) was added. The mixture was heated to dissolve the solids, and cooled to RT. The aqueous bottom layer was decanted (1.4 L water), and the organic phase was treated with active carbon (200 g) and filtered. The filtrate was concentrated to 3 L volume and cooled to −20 °C in a freezer. The solids were collected by filtration, rinsed twice with a mixture of EtOAc and MTBE (250 mL each at 0−4 °C), and dried under vacuum at 35−40 °C to produce the desired product (808 g, 36%). On large scale, it was not deemed economical to chromatographically isolate a second crop from the mother liquor, alhough a significant amount of the product was present.

3-Fluoro-6-methoxyquinoline (1). *Pd−C Method.* To 10% Pd/C (1 g) were added methanol (300 mL) and 2,4-dichloro-3-fluoro-6-methoxyquinoline (20 g, 0.0813 mol). After stirring for 30 min, the mixture was filtered through Celite (Note: This pretreatment was performed to remove an unidentified catalyst poison). To the filtrate were added fresh Pd/C (1 g) and ammonium formate (10 g). The reaction was stirred for 16 h at RT. The reaction mixture was filtered. The filtrate was stripped to dryness. The resulting residue was passed through a silica gel plug with 5% ethyl acetate in hexanes. Product-rich fractions were collected and concentrated to dryness to yield a white solid as the product (8.03 g, 56% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ (8.64 (d, J = 2.9 Hz, 1H), 7.98 (d, J = 9.1 Hz, 1H), 7.65 (dd, J = 9.1, 2.9 Hz, 1H), 7.31 (dd, J = 9.1, 2.9 Hz, 1H), 7.01 (d, J = 2.9 Hz, 1H), 3.92 (s, 3H). MS m/z 178.19 $(M + H)^+$. HRMS m/z Calcd for $C_{10}H_9NOF$ $(M + H)^+$ 178.0668, Found: 178.0656.

Raney Nickel Method. To a 20 L autoclave was charged MeOH (7 L), followed by the addition of **3b** (808 g, 3.28 mol) and 7 M NH_3 in MeOH (7 L). Raney nickel (150 g) was added, and the reaction was hydrogenated at 150 psi for 18 h. Portions of Raney nickel were added at intervals of 18 h (150 g), 42 h (100 g), and 50 h (50 g). The reaction was typically completed in 50−72 h. The reaction mixture was filtered through Celite and rinsed with MeOH (4 L) [Caution: Do not allow the filter bed to become dry at any time]. The filtrate was concentrated, and the resulting oil was dissolved in MTBE (600 mL). The solution was treated with active carbon at reflux and filtered. The hot filtrate was cooled slowly with agitation to form a thick slurry. The mixture was further cooled to −20 °C and filtered. The filter cake was rinsed with MTBE at −20 °C (2 × 100 mL) and dried to give the first crop of the desired product. A second crop of the product was recovered from the mother liquor by repeating the crystallization after concentration. Both crops were of similar purity by HPLC (>98%), and the combined yield was 489 g (81%). The batch size was repeated six times to give consistent results. Analytical data were identical to those obtained in the Pd/C reduction method.

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