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Regioselective Electrolytic 5,8-Difluorination of Quinolines

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Regioselective Electrolytic 5,8-Difluorination of Quinolines

An Honors Thesis submitted in partial fulfillment of the requirements for Honors in

Chemistry.

By
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Under the mentorship of Dr. Abid Shaikh

ABSTRACT

Over the past decade, synthesis of organofluorine compounds has become a mainstream research focus. The introduction of fluorine uniquely affects the biological properties of organic molecules such as making them more bioavailable, lipophilic and metabolically stable, and possibly increase the strength of a compound's interactions with a target protein. Approximately 30% of agrochemicals and 20% of pharmaceuticals contain fluorine, including commonly prescribed drugs such as Lipitor, Lexapro and Prozac. This work describes the development of a new methodology to incorporate fluorine into organic compounds. Our new method involves a regioselective electrochemical 5,8-difluorination of quinolines using HF:pyridine as both the reagent and supporting electrolyte. Various quinoline derivatives were subjected to electrolytic fluorination at room temperature to obtain moderate to good yields in a short reaction time of two hours.

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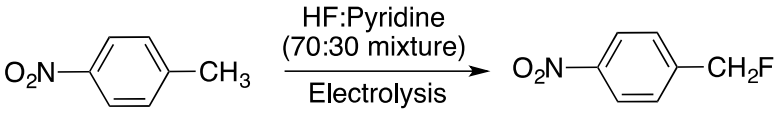
Introduction

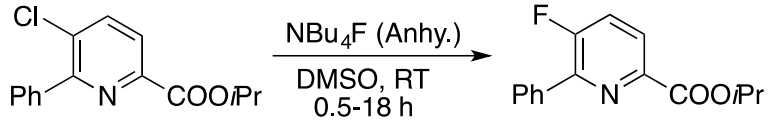
A biosynthetic pathway of incorporating fluorine into organic molecules was only discovered twelve years ago. O'Hagan et al.[1] demonstrated the enzymatic incorporation of fluoride to form fluoroacetate. The less evolved natural use of fluorine, compared to other halogens, is believed to be linked to the low solubility of most fluoride minerals; this sequestration of fluoride in inorganic compounds prevents biological accumulation and incorporation.[2]

Despite the absence of naturally fluorinated organic compounds, organofluorine chemistry has received extensive attention in recent years especially in the pharmaceutical industry and in materials science due to the unique properties of fluorinated compounds.[3] The strong electron-withdrawing effect of fluorine contributes to a number of biologically important molecular properties.[4] For example, it results in a significant increase in lipophilicity of the molecule, which is a very important feature for drug delivery as it increases the bioavailability of molecules traversing cellular membranes.[5] Because fluorine has a van der Waals radius comparable to that of hydrogen, 1.35 Å vs 1.20 Å, substituting hydrogen with fluorine does not impact recognition by protein binding sites.[6] The increased lipophilicity and a superior metabolic stability, compared to the use of methyl analogues, often accounts for an improved activity profile.[7] The different medicinal applications of fluorinated organic molecules are widespread; some of the most commonly utilized drugs are Prozac® (anti-depressant), Diflucan® (anti-fungal agent), Casodex® (anti-cancer agent), and Desflurane (inhalation anesthetic).[8] Recent applications of organofluorine compounds include potential therapeutics for HIV, cancer, and Alzheimer's disease.[9]

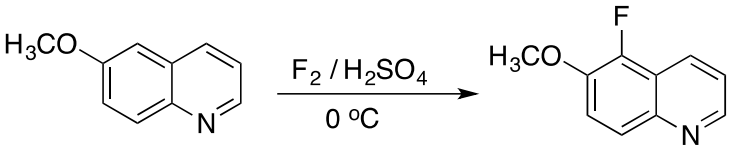
Accordingly, the synthesis of these molecules is in great demand and the search for new biologically active fluorinated compounds is in the forefront of organic and medicinal chemistry research.



LoBue *et. al. Microchemical Journal*, **1993**, *48*, 192-199.



Sanford *et. al. J. Org. Chem.* **2014**, *79*, 5827-5833.



Chambers *et. al. J. Fluorine. Chem.* **2002**, *117*, 99-101.

Figure 1. Literature overview of various fluorine incorporation methods.

The significance of fluorine incorporation into organic molecules has been well documented in the literature.[10] Despite the growing importance of fluorine-containing drugs, incorporation of a fluorine atom at a specified position of heterocycles still presents a challenge. Current reported methods involve the nucleophilic substitution of a chloride with a fluoride anion.[11] Even though the process involves mild reaction conditions, it still requires the synthesis of a chloride precursor. Ideally, the most straightforward approach to the synthesis would involve the transformation of a C-H bond to a C-F bond by using a widely available fluorinating reagent. Herein, we describe the use of HF:pyridine (Olah's reagent) for the synthesis of 5,8-difluoroquinolines. Previous investigations with

quinolines using elemental fluorine under acidic conditions (F_2/H_2SO_4) provided exclusively 5-fluoroquinoline product with a trace amount 5,8-difluoroquinoline.[12] Our synthetic strategy involves electrolysis using Olah's reagent as both the solvent and supporting electrolyte. This work demonstrates the successful extension of electrolytic fluorination method described by Savett (Figure 1).

Results and discussion

Our original goal was to achieve the acid-catalyzed C-H functionalization of quinaldine to incorporate fluorine. We started our study by choosing the reaction of quinaldine **1** with HF:pyridine (70:30) as the model. To our surprise, the fluorination product **3** at the 2-methyl position of quinoline was not observed. Instead, an unexpected 5,8-difluoro product **2** was obtained in 70% yield.

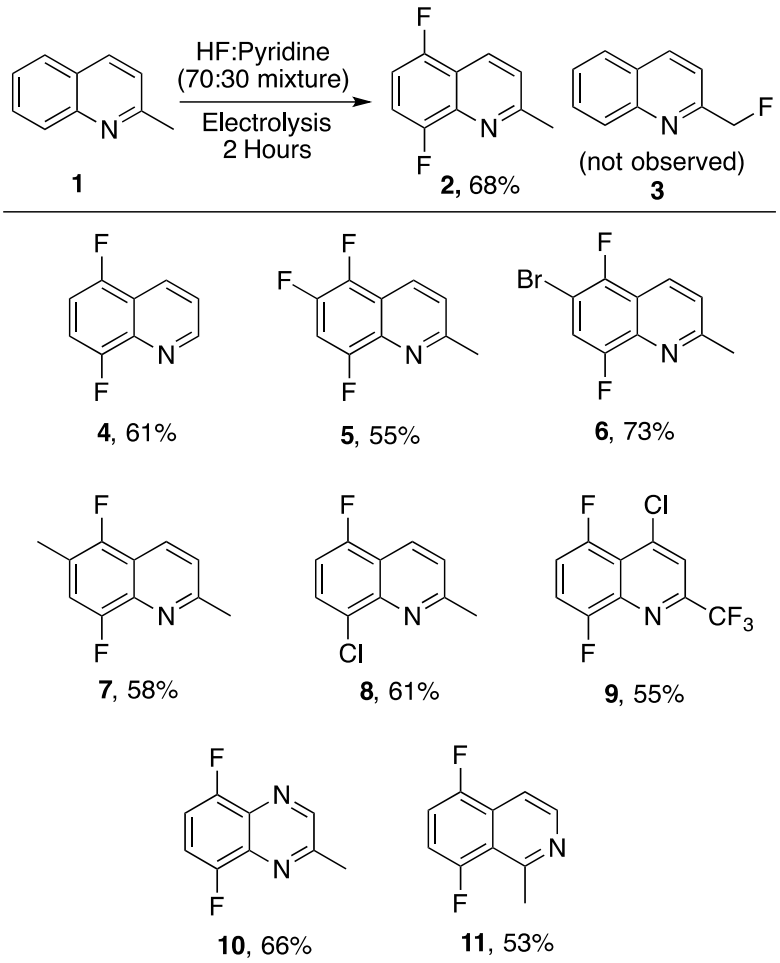


Figure 2. Regioselective difluorination of quinoline and its derivatives. Reaction conditions: 2-methylquinoline (100mg), HF:pyridine (4 mL), 2.4V, 2h.

Encouraged by this result, we further investigated the reaction to optimize the experimental conditions. The reaction proceeded rapidly at room temperature in higher yield. There was no significant improvement in the product yield observed even after an extended amount of time.

With the optimized conditions in hand, the scope of this reaction was further investigated with various substituted quinolines. Results showed that a wide range of substituted quinolines reacted smoothly to form the corresponding 5,8-difluoro products **4-11** (Figure 2). The substrates bearing a methyl group on the pyridinyl ring reacted to

produce good yields. In addition, 1-methylisoquinoline and 2-methylpyrazine substrates also afforded the expected products in good yields. Intriguingly, the reactions with halogenated quinolines, such as product **8,** provided the expected products without the loss of the original halogens. In each case, selective fluorination occurred on the benzenoid ring only; protonation of the heteroatom under the strong acidic reaction conditions causes deactivation of the heterocyclic ring.

To investigate the general efficacy of this method, we further investigated the fluorination of various complex molecules bearing the quinoline core. Biquinoline, acridine, and papaverine were subjected to electrolysis under similar reaction conditions as described above. Biquinoline provided the expected product **12** with fluorination occurring at both the quinoline rings. Acridine provided a 1,4,5,8-tetrafloroproduct **13** and papaverine provided the 5,8-difluoro product **14** (Figure 3).

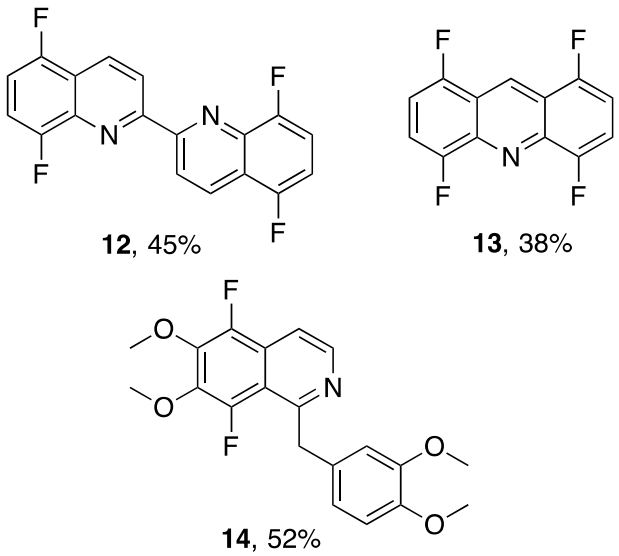


Figure 3. Regioselective difluorination of complex quinoline derivatives.

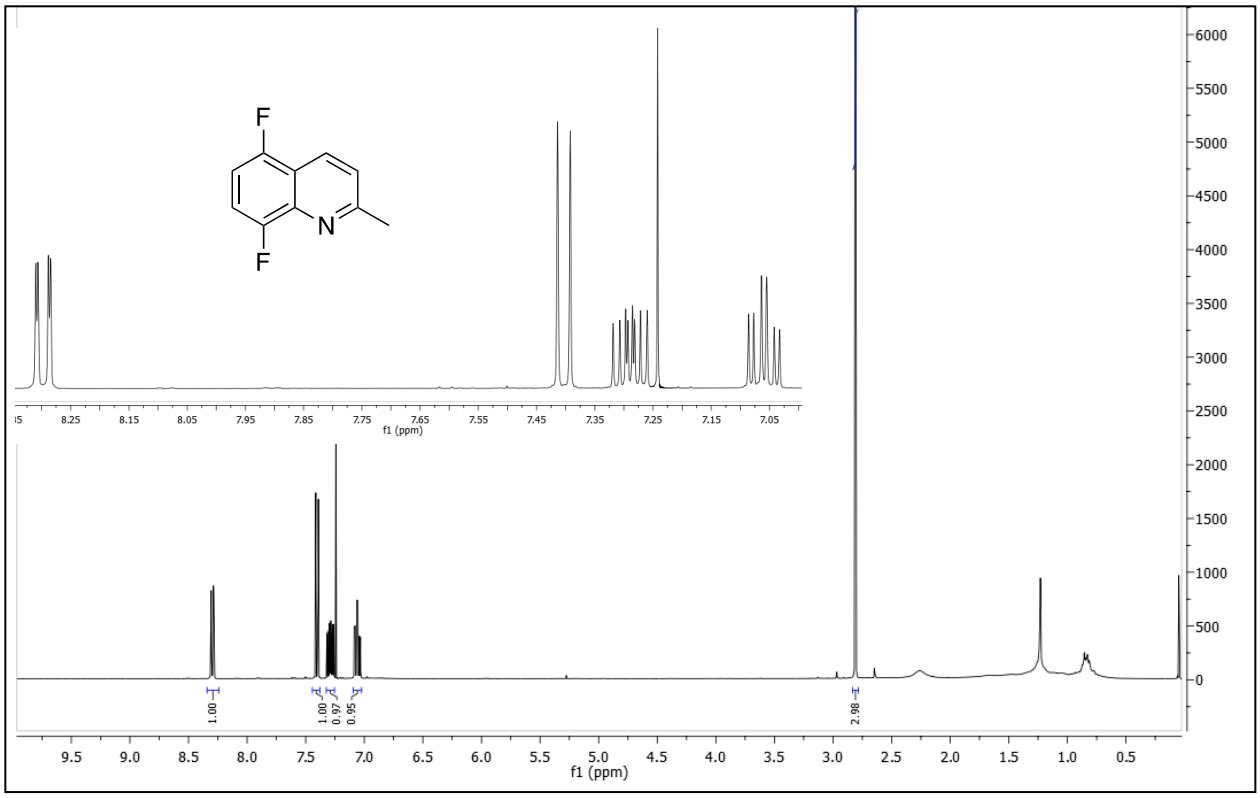


Figure 4. 1H NMR spectra of product 2 showed a unique pattern of signals in the aromatic range confirming the 5,8-difluorination occurred at the benzenoid ring.

Conclusion

In summary, we have developed a novel highly regioselective direct 5,8-difluorination of quinolines with Olah's reagent under electrolytic conditions. The methodology utilized in this experiment gave primarily moderate to good yields with various quinoline derivatives under mild reaction conditions and a short reaction time of two hours. This leads to the conclusion that this straightforward and effective reaction provides a new way to synthesize organofluorine compounds, which may open new possibilities in future chemical and biochemical applications.

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Appendix: Experimental Procedure and Product Characterization

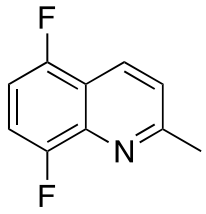
Experimental procedure

The quinoline (100mg) was transferred into a polypropylene syringe prepared by melting the barrel tip and adding a stir bar to form the reaction vessel. The quinoline was dissolved in 4 mL of HF:Pyridine, and the solution was stirred. The platinum electrodes were inserted into the reaction vessel, and an eDAQ ER466 potentiostat was used to push 100 mA in a repetitive step every five seconds alternating from -2.4V to 2.4V for two hours. After the reaction was complete, the excess acid was neutralized by adding the solution dropwise into a slurry of sodium bicarbonate. Once neutralized, the mixture was washed in ethyl

acetate, and the organics were isolated using a separatory funnel. The product mixture was filtered through anhydrous sodium sulfate and concentrated using a Buchi RotaVapor R-200. The crude mixture was dissolved in dichloromethane and purified using normal phase chromatography with a hexane/ethyl acetate system to obtain the expected compounds in high analytical purity. The product analysis and characterization using various spectral techniques was carried out and the data is summarized as below.

Product Characterization

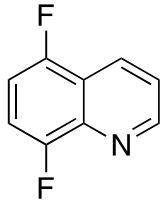
5,8-difluoro-2-methylquinoline (**2**)



Yellow-brown solid, m.p. 71.9-73.7°C

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 8.33 – 8.27 (m, 1H), 7.42 – 7.38 (m, 1H), 7.32 – 7.26 (m, 1H), 7.09 – 7.02 (m, 1H), 2.81 (s, 3H), ^{19}F-NMR (376.22 MHz, $CDCl_3$ δ (ppm) -127.16 – -127.30 (m, *1F*), -130.03 – -130.36 (m, 1*F*)

5,8-difluoroquinoline (**4**)

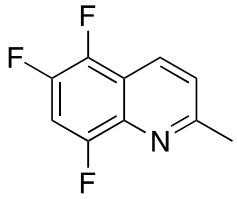


Red-brown liquid

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 8.94 – 8.88 (m, 1H), 8.15 – 8.10 (m, 1H), 7.62 – 7.57 (m, 1H), 6.58 – 6.46 (m, 2H)

^{19}F-NMR (376.22 MHz, $CDCl_3$ δ (ppm) -87.64 (m, 1F), -94.86 (m, 1F)

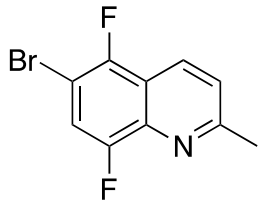
5,6,8-trifluoro-2-methylquinoline (**5**)



Yellow liquid

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 7.89-7.85 (m, 1H), 7.24-7.16 (m, 1H), 6.91-6.87 (m, 1H), 6.31-6.23 (m, 1 H), 2.58 (s, 3H), ^{19}F-NMR (376.22 MHz, $CDCl_3$ δ (ppm) -120.65 – -120.76 (m, 1F), -120.99 – -121.12 (m, 1F)

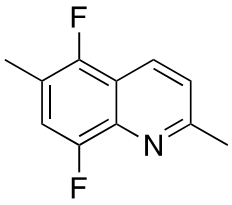
6-bromo-5,8-difluoro-2-methylquinoline (**6**)



Yellow solid, m.p. 125.5-127.91°C

^{1}H-NMR (400 MHz, CDCl3) δ (ppm) 8.26 – 8.22 (m, 1H), 7.50 – 7.45 (m, 1H), 7.42 – 7.38 (m, 1H), 2.76 (s, 3H), ^{19}F-NMR (376.22 MHz, $CDCl_3$ δ (ppm) -120.41 – -120.54 (m, 1F), -128.22 – -128.35 (m, 1F)

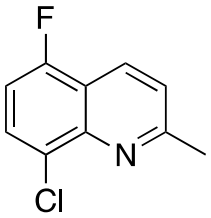
5,8-difluoro-2,6-dimethylquinoline (**7**)



Yellow liquid

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 7.95 – 7.91, 7.35 – 7.32 (m, 1H), 5.89 – 5.67 (m, 1H), 5.07 – 4.82 (m, 1H), 2.68 (d, *J* = 2.0 Hz, 3H), 1.77 (t, *J* = 15.6 Hz, 3H)

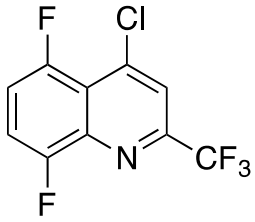
8-chloro-5-fluoro-2-methylquinoline (**8**)



Yellow-brown liquid

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 8.01 – 7.95, 7.41 – 7.37 (m, 1H), 7.92 – 7.89, 7.27 – 7.24 (m, 1H), 6.73 – 6.66, 6.30 – 6.23 (m, 1H), 5.35 – 5.16 (m, 1H), 2.68 (d, *J* = 21.4 Hz, 3H)

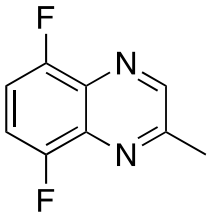
4-chloro-5,8-difluoro-2-(trifluoromethyl)quinolone (**9**)



Light orange solid, m.p. 60.3-62.4°C

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 7.87 – 7.86 (m, 1H), 7.52 – 7.46, 7.39 – 7.32 (m, 1H), 6.61 – 6.47 (m, 1H), ^{19}F-NMR (376.22 MHz, $CDCl_3$ δ (ppm) -67.88 – -67.90 (m, 1F)

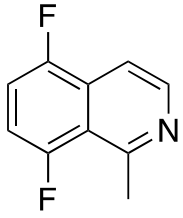
5,8-difluoro-2-methylquinoxaline (**10**)



Red-pink solid, m.p. 68.8-72.3°C

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 8.76 (s, 1H), 7.44 – 7.41 (m, 1H), 7.35 – 7.32 (m, 1H), 3.40 (s, 1H), ^{19}F-NMR (376.22 MHz, $CDCl_3$ δ (ppm) -95.27 – -95.36 (m, 1F), -95.54 – -95.63 (m, 1F)

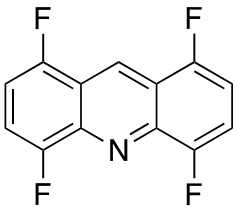
5,8-difluoro-1-methylisoquinoline (**11**)



Yellow-white solid, m.p. 81.7-83.1°C

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 8.44 – 8.40 (m, 1H), 7.66 – 7.61 (m, 1H), 7.23 – 7.17 (m, 1H), 7.13 – 7.04 (m, 1H), 3.02 (d, J = 7.0 Hz, 3H), ^{19}F-NMR (376.22 MHz, $CDCl_3$ δ (ppm) -113.35 – -113.57 (m, 1F), -126.44 – -126.56 (m, *J* = 22.9, 8.9, 4.3 Hz, 1F)

1,4,5,8-tetrafluoroacridine (**13**)



Yellow solid, m.p. 113.3-115.9°C

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 9.32 – 9.01 (m, 1H), 8.11 – 8.02 (m, 1H), 7.88 – 7.55 (m, 1H), 7.49 – 7.32 (m, 1H), 7.21 – 7.15 (m, 1H), 7.13 – 6.39 (m, 1H), 5.99 – 5.80 (m, 1H)