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Synthesis of novel fluorinated 4-aminoquinoline derivatives

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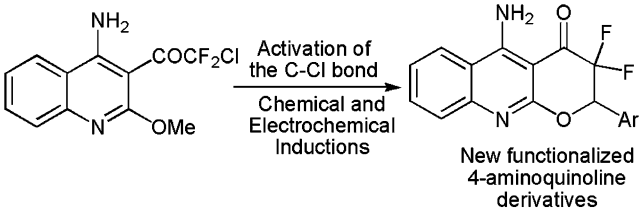
Abstract—New 4-aminoquinolines having a $-CF_2CH-$(heteroaryl)–OH moiety are obtained in moderate yields from the electrochemical catalyzed reaction of the corresponding 4-amino-3-chlorodifluoroacetyl-2-methoxyquinoline in the presence of heteroaryl aldehydes. A one-pot intramolecular zinc mediated aromatic nucleophilic substitution also gave access to novel difluorinated 5-aminodihydropyrano[2,3-*b*]quinolin-4-ones.

There continues to be an interest in the synthesis of new *gem*-difluorinated compounds because of the potential biological properties of such molecules.[1] For example, electrophilic carbonyl derivatives, such as α,α-difluoroketones, are compounds of great interest because they have the capability to form stable adducts (such as hydrates and hemiketals) with nucleophiles;[1] it is believed that this property allows some fluorinated ketones to mimic the transition states involved in the hydrolytic action of many enzymes.[1] In addition, the difluoromethylene moiety (CF_2) is a key structural unit in many fluorinated compounds of biological and pharmaceutical significance. Fluorine substituted aromatics and heterocycles may find broad applications such as agrochemicals, anticancer, and antiviral agents.[2] Quinolines are important heterocyclic systems, constituting the structure of many naturally occurring products and having interesting pharmacological properties.[3] In particular quinolylamine derivatives have been used as the basis in the molecular design for synthetic antimalarial compounds,[4] anti-HIV agents,[5] and for the treatment of Alzheimer's disease.[6] Recently, we have been interested in the aromatic nucleophilic substitution reactions of *N*,*N*-dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine,[7] *N*,*N*-dimethyl-2-trifluoroacetyl-4-halo-1-naphthyl-amines,[8] *N*,*N*-dimethyl-5,7-bis(trifluoroacetyl)-8-quinolylamine,[9] with amines, thiols, and alcohols and we have shown that the corresponding exchanged products could be easily converted to various fluorinated fused-heterocycles of potential biological importance. Recently these aromatic nucleophilic substitution reactions were extended to *N*,*N*-dimethyl-2-trifluoroacetyl-1-naphthylamine.[10] As part of our ongoing efforts in search of synthetic approaches for the synthesis of fluorinated compounds with potential biological and synthetic applications,[11] we wish to present a method to prepare, new $-CF_2CHOH-$ derivatives that incorporate a 4-aminoquinoline unit. In addition a one-pot process for the synthesis of novel difluorinated 5-amino dihydropyrano[2,3-*b*]quinolin-4-one products is presented (Scheme 1).

Our major goal was to find the conditions to obtain an efficient way to prepare new 4-aminoquinoline structures



Scheme 1.

Keywords: Zinc; Electrochemistry; Fluorine; Reformatsky; 4-Aminoquinoline; S_NAr.
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for biological evaluation; these new difluoromethylene heterocycles were designed as part of a project devoted to the synthesis and biological evaluation of fluorinated analogs of reported potential antiviral agents, and memory enhancing agents (for potential application for the treatment of Alzheimer disease; Fig. 1). For example, some 2,3-dihydropyrano[2,3-*b*]pyridine structures have been evaluated as new acetylcholinesterase inhibitor analogs of TACRINE (THA),[12] or have demonstrated some in vitro antiviral activity.[13]

Our starting material, 4-amino-3-chlorodifluoroacetyl-2-methoxyquinoline **3** was synthesized in three steps (Scheme 2). Chlorodifluoroacetylation of methyl orthoacetate [chlorodifluoroacetic anhydride (CDFAA)/pyridine in anhydrous CH_2Cl_2] followed by O–N exchange reaction of the resulting 1-chloro-1,1-difluoro-4,4-dimethoxybut-3-en-2-one **1** with 2-aminobenzonitrile in refluxing MeCN afforded 1-chloro-1,1-difluoro-4-methoxy-4-(2-cyanophenyl)aminobut-3-en-2-one **2**. The much deshielded peak of the amino proton at $\delta_H =$ 12.03–12.60 ppm due to hydrogen bonding between NH and C=O indicated *E* configuration. Compound **2** was then cyclized in refluxing CF_3SO_3H for 5 min to give the corresponding **3** in a modest 34% isolated yield.[14] Other acids were tested such as CF_3CO_2H, CH_3CO_2H, $C_2H_5CO_2H$, HCl, H_2SO_4, but they either afforded no desired target or gave very complex mixtures. Careful examination, by cyclic voltammetry, of the reduction potential of starting material **3** ($Ep_{c1} = -1.27$ V vs SCE, first peak potential measured in DMF/0.1 M NBu_4PF_6), indicated that this substrate might be a good electron-acceptor, and this therefore prompted us to use electron-transfer activation for the in situ generation and trapping of the corresponding α,α-difluoroacetyl anion with a series of aromatic and heterocyclic aldehydes. Since we have already developed some useful carbon–carbon bond forming reactions between aromatic and heterocyclic chlorodifluoromethylated ketones and unsaturated compounds, by utilizing tetrakis(dimethylamino)ethylene (TDAE)[15] as a synthetic electron-transfer reagent or electrochemical reduction, we first intended to apply these electron-transfer induced approaches to the coupling reaction of **3** and benzaldehyde.

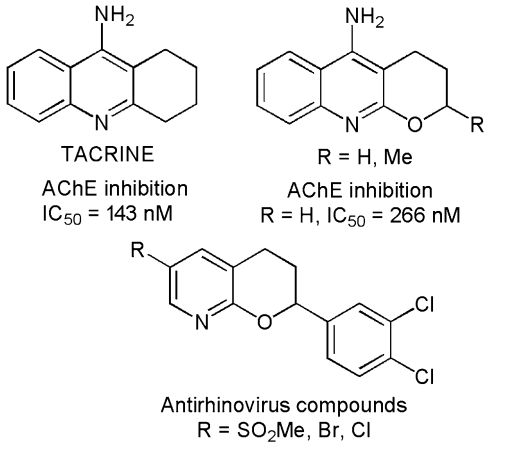
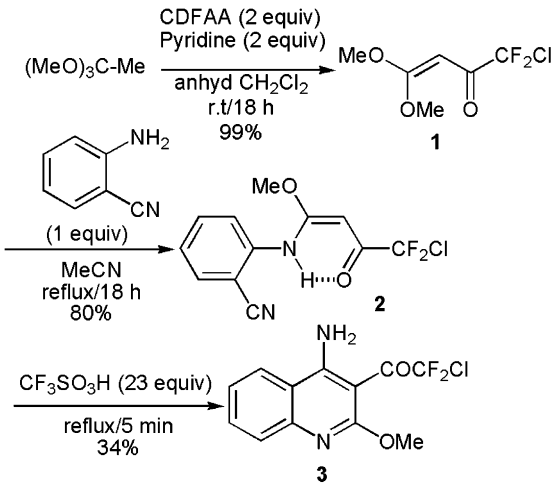


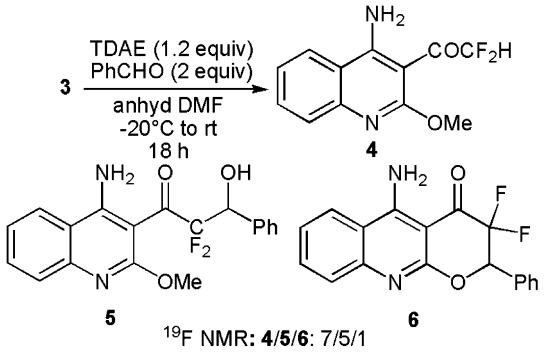
Figure 1. 2,3-Dihydropyrano[2,3-*b*]pyridine structures of biological importance.



Scheme 2.

Using our usual conditions, 1.2 equiv of TDAE was added dropwise to 1 equiv of ketone **3** and 2 equiv of PhCHO in anhydrous DMF at −20 °C, warming to room temperature reaction and then stirring at room temperature for 18 h, led to rather disappointing results, with reduction product **4** being the major component (54% ^{19}F NMR yield, with $PhOCF_3$ as internal standard); alcohol **5** was also formed along with another *gem*-difluorinated product in a 5/1 ratio as minor components. Other fluorinated impurities were also observed in the crude reaction mixture. Isolation and characterization of the third compound, demonstrated that it was the cyclized structure **6** (12% isolated yield),[16] resulting from an intramolecular displacement of the OMe group (Scheme 3).

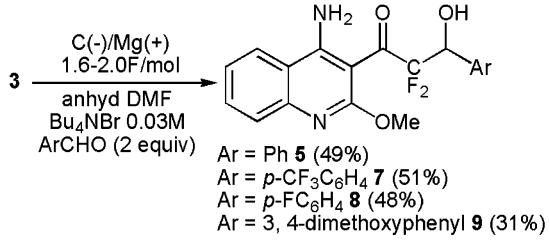
When the reaction was conducted in PhCHO as solvent and electrophile, it was cleaner but yields of **5** and **6** were not improved. Indium has been found to be a suitable reagent for the coupling reactions of β-aminovinyl chlorodifluoromethylated ketones with a series of heteroaldehydes.[17] However using our described conditions [In 1.2 equiv, PhCHO 1.2 equiv, THF/H_2O (1/4, v/v) at room temperature for 18 h], starting material **3** was



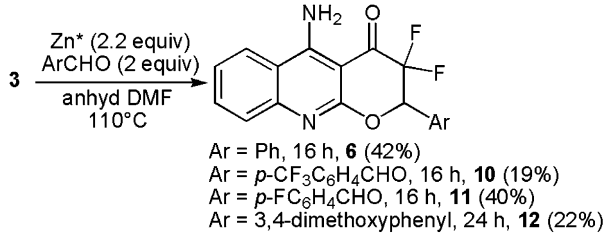
Scheme 3.

recovered with no fluorinated products being formed. Strong binding of nitrogen atoms at the indium center may be an explanation for this disappointing result. Electrochemical activation of substrate **3** in the presence of 2 equiv of PhCHO, using an undivided cell (carbon felt cathode/magnesium anode, at room temperature) at controlled potential electrolysis corresponding to the first peak potential measured by cyclic voltammetry, afforded cleanly the reduction product **4** and alcohol adduct **5** in a 1/2 ratio with a consumption of electricity close to 1.6 F/mol. None of the cyclized product **6** was observed. Product **5** was isolated after silica gel chromatography in 49% isolated yield as a viscous yellowish oil. The electrolysis reaction was also extended with other aldehydes to yield the corresponding alcohol adducts in moderate yields (Scheme 4).[18]

The Reformatsky reaction of halogenodifluoromethyl ketones with carbonyl compounds mediated by zinc[1,19] is one of the well-known synthetic methodologies to obtain the corresponding carbon–carbon coupling products. Using 2.2 equiv of acid washed, activated zinc, and 2 equiv of PhCHO in anhydrous DMF at 110 °C (oil bath temperature) for 16 h, starting material **3** was totally consumed and gave the cyclized compound **6** as major product (42% isolated yield) along with reduction product **4** (Scheme 5).[20] ^{19}F NMR monitoring clearly indicated that **5** was an intermediate and that it was subsequently transformed into **6**. This approach was then applied to other aldehydes. When using *p*-$CF_3C_6H_4CHO$, cyclized product **10** was obtained in 19% isolated yield because of partial decomposition during silica gel chromatography (^{19}F NMR yield using $PhOCF_3$ as internal standard was close to 38%). In addition pinacol coupling product was observed by ^{19}F NMR ($\delta_F = -62.1$ ppm). With *p*-FC_6H_4CHO, some pinacol was also formed but in lesser amount, and cyclized product **11** could be obtained in 40% isolated yield. With 3,4-dimethoxybenzaldehyde, reaction was slower (24 h) with a 22% isolated yield of **12**. An increased amount of activated zinc (4 equiv) resulted in shorter reaction time but the final product unfortunately had decomposed into unidentified fluorinated compounds.



Scheme 4.



Scheme 5.

In conclusion we have demonstrated that the method used to activate the C–Cl bond of a suitable 4-amino-3-chlorodifluoroacetyl-2-methoxyquinoline, can lead to different types of fluorinated 4-aminoquinoline derived products.

Under electrochemical activation, *gem*-difluorinated alcohol adducts can be obtained in reasonable yields, whereas a Reformatsky type reaction gave directly *gem*-difluorinated 5-aminodihydropyrano[2,3-*b*]quinolin-4-one cyclized products in modest yields. The yields of the products **5**–**12** need to be improved, but using the present methodology has been adequate for preparation of these novel molecules in sufficient quantity for biological screening. We are currently trying to optimize the yields of the dihydropyrano[2,3-*b*]quinolines as well as to extend these reactions with other electrophiles and new chlorodifluoromethylated heterocyclic substrates. The products described in this letter are currently being screened as potential acetylcholinesterase inhibitors and antivirals.

Acknowledgments

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14. *1-Chloro-1,1-difluoro-4,4-dimethoxybut-3-en-2-one* (**1**). To a stirred solution of methyl orthoacetate (12.02 g, 10.0 mmol) and pyridine (1.62 ml, 20.0 mmol) in CH_2Cl_2 (20 ml) was added dropwise chlorodifluoroacetic anhydride (3.48 ml, 20.0 mmol) and the mixture was stirred at room temperature for 18 h. CH_2Cl_2 (20 ml) was added to the reaction mixture and then it was washed with aqueous 10% Na_2CO_3 (50 ml) and with H_2O (2×50 ml) and the organic layer was separated and dried (Na_2SO_4). The solvent was removed in vacuo to give practically pure product **1** (1.99 g, 99%). Mp 48–49 °C (hexane/EtOAc). ^1H NMR ($CDCl_3$): δ_H 5.10 (s, 1H, CH), 4.07 (s, 3H, CH_3), 4.03 (s, 3H, CH_3). ^{19}F NMR ($CDCl_3$/$CFCl_3$): δ_F −67.5 (2F, s). IR (KBr) $\nu_{C=O} = 1680\ cm^{-1}$. Anal. Calcd for $C_6H_7ClF_2O_3$: C, 35.93; H, 3.52. Found: C, 35.73; H, 3.61. *(E)-1-Chloro-1,1-difluoro-4-methoxy-4-(2-cyano-phenyl)-aminobut-3-en-2-one* (**2**). To a solution of **1** (1.00 g, 5.0 mmol) in MeCN (10 ml) was added 2-aminobenzonitrile (0.6 g, 5.05 mmol) and the mixture was stirred under reflux for 18 h. The solvent was removed in vacuo and the crude mixture was recrystallized from hexane/EtOAc to afford **2** (1.15 g, 80%). Mp 143–144 °C (hexane/EtOAc); ^1H NMR ($CDCl_3$): δ_H 12.60–12.03 (br, 1H, NH), 8.03–7.23 (m, 4H, C_6H_4), 5.53 (s, 1H, CH), 4.08 (s, 3H, CH_3). ^{19}F NMR ($CDCl_3$/$CFCl_3$): δ_F −64.7 (2F, s). IR (KBr) $\nu_{NH} = 3463$, $\nu_{CN} = 2226$, $\nu_{C=O} = 1639\ cm^{-1}$. Anal. Calcd for $C_{12}H_9ClF_2N_2O_2$: C, 50.28; H, 3.16; N, 9.77. Found: C, 50.41; H, 3.02; N, 9.78. *4-Amino-3-chlorodifluoroacetyl-2-methoxyquinoline* (**3**). Trifluoromethanesulfonic acid (3.2 ml, 36 mmol) was added to compound **2** (450 mg, 1.57 mmol) and the reaction mixture was refluxed with stirring for 5 min. Saturated aqueous solution of Na_2CO_3 (50 ml) was added to the reaction mixture, then aqueous mixture was extracted with EtOAc (50 ml), and the organic layer was separated and dried (Na_2SO_4). The solvent was evaporated in vacuo and the crude mixture was purified by silica gel chromatography using hexane/EtOAc (10/1) as eluent to give **3** (151 mg, 34%). Mp 136–137 °C (hexane/EtOAc). ^1H NMR ($CDCl_3$): δ_H 8.30–7.26 (m, 6H, H-5, H-6, H-7, H-8, NH_2), 4.17 (s, 3H, CH_3). ^{19}F NMR ($CDCl_3$/$CFCl_3$): δ_F −61.5 (2F, s). IR (KBr) $\nu_{NH} = 3461$, 3338, $\nu_{C=O} = 1603\ cm^{-1}$. Anal. Calcd for $C_{12}H_9ClF_2N_2O_2$: C, 50.28; H, 3.16; N, 9.77. Found: C, 50.47; H, 3.32; N, 9.42.
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16. A typical procedure for the reaction between **3**, TDAE and benzaldehyde is as follows: Into a two-necked flask equipped with a silica gel drying tube and a nitrogen inlet were added, under nitrogen at −20 °C, a 5 ml anhydrous DMF solution of **3** (0.436 g, 1.52 mmol) and benzaldehyde (0.32 g, 3.04 mmol; 0.15 ml). The solution was stirred and maintained at this temperature for 30 min and then was added dropwise (via a syringe) the TDAE (0.30 g, 1.52 mmol, 0.15 ml). A red color immediately developed with the formation of a white fine precipitate. The solution was vigorously stirred at −20 °C for 1 h and then warmed up to room temperature for 18 h. After this time fluorine NMR showed that the ketone **3** was totally consumed. The orange-red turbid solution was filtered (to remove the octamethyloxamidinium dichloride) and hydrolyzed with 30 ml of H_2O. The aqueous solution was extracted with $CHCl_3$ (3×30 ml), the combined organic solutions washed with brine (3×30 ml), H_2O (3×30 ml), and dried over Na_2SO_4. Evaporation of the solvent left an orange viscous liquid as crude product. Purification by silica gel chromatography (EtOAc/Petroleum ether, 90/10 as eluent) gave first **4**, with **5** and **6** as the most polar compounds. *1-(4-Amino-2-methoxyquinolin-3-yl)-2,2-difluoro-3-hydroxy-3-phenyl-propan-1-one* (**5**). Yellowish viscous oil. ^1H NMR ($CDCl_3$): δ_H 4.07 (3H, s, OMe), 5.55 (1H, dd, $J = 18.1$, 6.40 Hz, –C*H*OH), 7.02 (2H, br s, NH_2), 7.29–7.71 (9H, m). ^{19}F NMR ($CDCl_3$/$CFCl_3$): δ_F −108.5 (1F, dd, $J = 266.2$, 6.90 Hz), −119.7 (1F, dd, $J = 266.2$, 18.3 Hz). HRMS: Calcd for $C_{19}H_{16}F_2N_2O_3$ 358.1129, Found 358.1135. *5-Amino-3,3-difluoro-2-phenyl-2,3-dihydropyrano[2,3-b]quinolin-4-one* (**6**). Yellow solid. Mp 161–164 °C (decomp). ^1H NMR ($CDCl_3$): δ_H 5.87 (1H, d, $J = 20.8$ Hz), 6.99–8.12 (11H, m). ^{19}F NMR ($CDCl_3$/$CFCl_3$): δ_F −121.6 (1F, dd, $J = 283.3$, 21.8 Hz), −125.3 (1F, d, $J = 283.3$). ^{13}C NMR (DMSO-d_6) δ_C 80.1, 117.3, 125.2, 128.6 (t, $^1J_{C-F} = 279.1$ Hz), 129.1, 129.4, 129.6 (t, $^2J_{C-F} = 10.7$ Hz), 130.2, 130.5, 131.9, 132.5, 133.0, 134.9, 145.1, 148.9, 159.5, 161.7, 181.7 (C=O, $^2J_{C-F} = 33.4$ Hz). HRMS: calcd for $C_{18}H_{12}F_2N_2O_2$ 326.0867, Found 326.0923.
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18. A typical procedure for the electrochemical coupling of **3** and benzaldehyde is as follows: The reaction was conducted in an undivided cylindrical Pyrex cell, fitted with a carbon felt cathode ($S = 15\ cm^2$) and a magnesium rod as anode under nitrogen. Starting material **3** (0.436 g, 1.52 mmol) was added to a solution of anhydrous DMF (40 ml) containing NBu_4Br (0.38 g, 1.18 mmol) and benzaldeyhde (0.32 g, 3.04 mmol; 0.15 ml). The electrolysis was performed under a constant current ($I = 0.035$ A) till 1.6–2 F/mol of electricity had passed. The solution was hydrolyzed with saturated aqueous NaCl (60 ml) and the organic portion was extracted with ethyl acetate (3×60 ml). The combined organic layers were washed with saturated aqueous NaCl (3×60 ml), water (3×60 ml), and dried over Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure left a residue, which was purified by silica gel chromatography using petroleum ether/EtOAc (90/10) as eluent to give compounds **5**–**9**.
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20. A typical procedure for the reaction of **3**, benzaldehyde and zinc is as follows: Into a two-necked flask equipped with a reflux condenser and a nitrogen inlet were added, under nitrogen, a 10 ml anhydrous DMF solution of **3** (0.436 g, 1.52 mmol) and benzaldehyde (0.32 g, 3.04 mmol; 0.15 ml). The solution was stirred at room temperature until complete dissolution and then was added activated zinc at once (0.198 g, 3.04 mmol). The yellowish solution was then heated at 110 °C (oil bath temperature) for 16–24 h until all starting ketone **3** was consumed (^{19}F NMR monitoring). The dark-brown mixture was cooled down to room temperature, filtrated, and DMF was evaporated to dryness. The crude product was diluted with EtOAc and the organic solution was washed with a saturated aqueous NH_4Cl solution (3×30 ml), and dried over Na_2SO_4. Evaporation of the solvent left a viscous oil as crude product. Purification by silica gel chromatography using petroleum ether/EtOAc (90/10) as eluent gave the products **6**–**12**.