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Tetrahedron Letters 46 (2005) 7817–7821
Tetrahedron Letters

Synthesis of novel fluorinated 4-aminoquinoline derivatives

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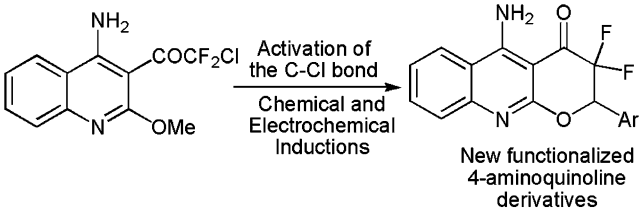
Received 1 July 2005; revised 30 August 2005; accepted 6 September 2005
Available online 21 September 2005

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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doi:10.1016/j.tetlet.2005.09.018

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.

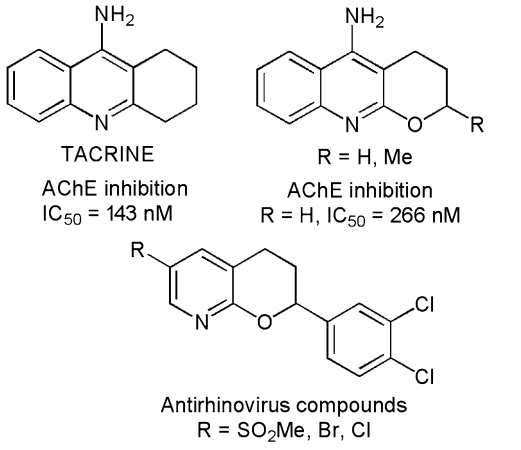
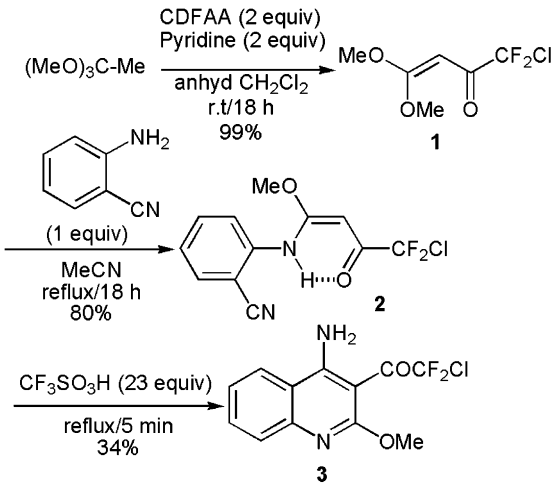


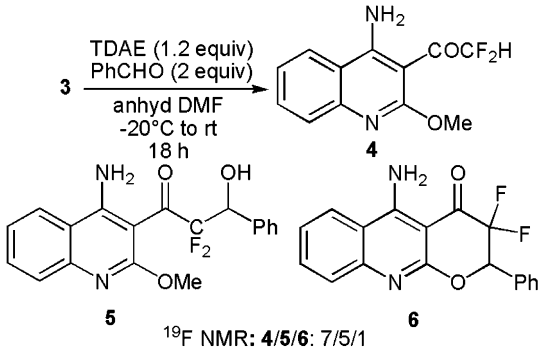
Figure 1. 2,3-Dihydropyrano[2,3-*b*]pyridine structures of biological importance.



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.