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Synthesis of novel fluorinated 4*H*-benzo[*h*]chromen-4-one and 4*H*-pyrano[3,2-*h*]quinolin-4-one derivatives

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This Letter is dedicated to the memory of Professor Yoshihiro Matsumura

Abstract

New fluorinated 4*H*-benzo[*h*]chromen-4-one and 4*H*-pyrano[3,2-*h*]quinolin-4-one derivatives are obtained in moderate to good yields, through a one-pot aldolization–intramolecular S_NAr process, from the tetrakis(dimethylamino)ethylene (TDAE) mediated reductive cleavage of two *N*,*N*-dimethylamino-bis-chlorodifluoroacetyl substrates in the presence of heteroaryl aldehydes.

Keywords: Tetrakis(dimethylamino)ethylene; Electron transfer; Fluorine; Flavone; S_NAr

Fluorinated substituted aromatics and heterocycles have found broad applications such as agrochemicals, anticancer and antiviral agents.[1] The similarity in size makes fluorine an obvious candidate to replace hydrogen, often without significant disturbance of the molecular geometry and shape.[2] Flavonoids form a class of benzo-γ-pyrone derivatives which are common in plants. They possess a wide spectrum of biological activities. Most notably flavonoids have been found to possess anticancer activities.[3] Recently, some derivatives have been evaluated as potential anti-HIV agents for the treatment of AIDS.[4] Fluorinated flavones have been rarely described in the literature. Fuchigami and co-workers described the electrochemical partial mono-fluorination of a series of 6-substituted flavones to yield the corresponding 3-fluoro-6-substituted flavones in moderate yields.[5] The same group extended their studies to the electrolytic partial fluorination of (*E*)-3-benzylidene-2,3-dihydrochroman-4-ones.[6] Laurent and co-workers also reported the anodic fluorination of 2-phenylthiochromen-4-one to give the corresponding mono-fluorinated product in 46% yield.[7] More recently some B-Ring fluorinated flavonoids have been screened as potential telomerase inhibitors;[3a] one compound showed a very promising activity ($IC_{50} = 0.6$ μM), comparable to the analog lacking the fluorine atom. In addition B-Ring trifluoromethylated flavonoids have been prepared and tested in vitro against cancer cell lines (Fig. 1).[8] For some years we have been interested in the aromatic nucleophilic substitution reactions of *N*,*N*-dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine,[9] *N*,*N*-dimethyl-2-trifluoroacetyl-4-halo-1-naphthyl-amines,[10] *N*,*N*-dimethyl-5,7-bis(trifluoroacetyl)-8-quinolylamine,[11] with amines, thiols and alcohols and we have shown that the corresponding exchanged products could be easily converted to various

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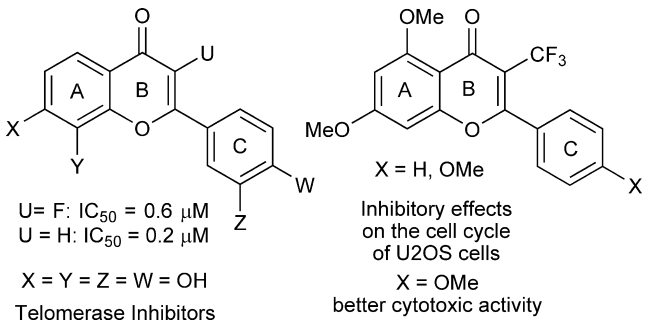


Fig. 1. Biologically active fluorinated and trifluoromethylated flavonoids.

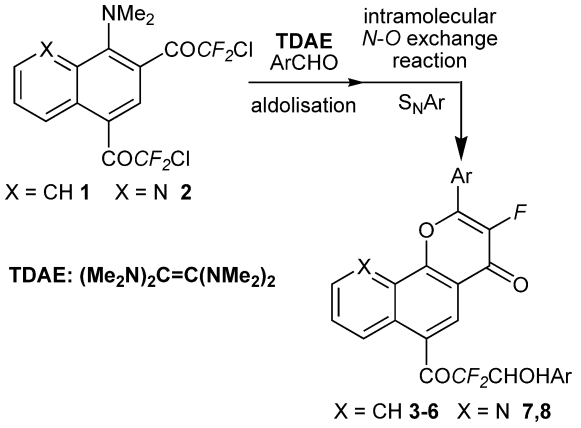
fluorinated fused-heterocycles of potential biological importance. Recently, these aromatic nucleophilic substitution reactions were extended to *N*,*N*-dimethyl-2-trifluoroacetyl-1-naphthylamine.[12]

As part of our ongoing efforts in search of synthetic approaches for the synthesis of novel fluorinated heterocycles with potential biological applications, we envisaged to prepare novel fluorinated fused flavone-type derivatives **3**–**8**, utilizing the tetrakis(dimethylamino)ethylene (TDAE)[13] reagent and *N*,*N*-dimethyl-2,4-bis(chlorodifluoroacetyl)-1-naphthylamine **1** and *N*,*N*-dimethyl-5,7-bis(chlorodifluoroacetyl)-8-quinolylamine **2** as model substrates, in the presence of aromatic and heteroaldehydes (Scheme 1). In addition, and relevant to the work presented in this Letter, we also described an approach to the synthesis of novel difluorinated 5-aminodihydropyrano[2,3-*b*]quinolin-4-ones through a one-pot zinc mediated aldolization–intramolecular S_NAr process.[14] Our targets can be regarded as analogs of α-naphthoflavone and derivatives, known for their anticancer activities,[15] as potential cystic fibrosis transmembrane conductance regulators,[16] adenosine receptor antagonists,[17] and potent antiplatelet.[18] We wish to present herein our preliminary results.

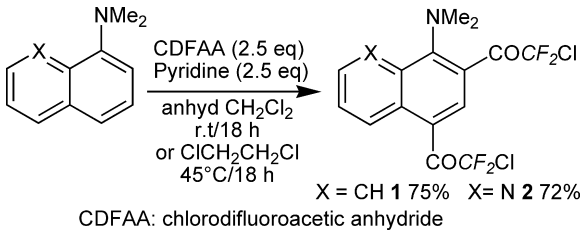
Substrate **1** was conveniently prepared in a 75% isolated yield, by bis-chlorodifluoroacetylation of the commercially available *N*,*N*-dimethyl-1-naphthylamine, using 2.5 equiv of chlorodifluoroacetic anhydride (CDFAA) and pyridine in anhydrous CH_2Cl_2 at room temperature for 18 h. Substrate **2** was similarly prepared in a 72% isolated yield, using *N*,*N*-dimethyl-8-quinolylamine[13e] as starting material, in $ClCH_2CH_2Cl$ as solvent, at 45 °C for 18 h (Scheme 2).

Careful examination, by cyclic voltammetry of the reduction potential of starting materials **1** and **2** (in DMF + 0.1 M NBu_4PF_6), indicated that these substrates were reduced at relatively low potentials ($E_1 \sim -1.1$ V vs SCE), suggesting that they were good-electron acceptors and that they may be effectively reduced by TDAE. Usually the reduction potential corresponding to the reductive cleavage of the two C–Cl bonds is very close (~100 mV) with the one from the chlorodifluoroacetyl moiety at the *para* position of the $-NMe_2$ group being the more positive.

When 2.2 equiv of TDAE (to generate the bis-enolate) was added dropwise to 1 equiv of ketone **1** and 4 equiv of PhCHO in anhydrous DMF at −20 °C, the familiar dark red colour of the charge transfer complex appeared. When the addition of TDAE was completed, the mixture was then stirred at −20 °C for 1 h and slowly warmed to room temperature over 1 h. TLC analysis of the reaction mixture (orange-brown with some insoluble solid) revealed that some starting material was still present in addition with several products. Fluorine NMR analysis revealed besides the presence of unreacted ketone **1**, the formation of *N*,*N*-dimethyl-2,4-bis(difluoroacetyl)-1-naphthylamine as the major component, as well as the presence of two other products characterized by two doublets of doublets. In addition two singlets were observed at δ_F close to −57 ppm/$CFCl_3$ and −159.60 ppm/$CFCl_3$. These rather disappointing results indicated that the reduction and protonation of the bis-enolate was the major pathway. Optimization of the reaction conditions showed that a large excess of the aldehyde (8 equiv) was necessary, as well as a longer reaction time (2 h at −20 °C followed by 3 h at room temperature) for complete consumption of starting material, cleaner reaction and higher yield of cyclized products. Using 8 equiv of PhCHO, 1 equiv of ketone **1** and 2.2 equiv of TDAE, and after warming-up the solution to room temperature over 3 h, the solution was quenched with brine and the resulting copious precipitate was extracted with EtOAc. Evaporation of the organic extracts and trituration of the oily residue with cyclohexane (to remove unreacted benzaldehyde) left an orange solid. Fluorine NMR analysis



Scheme 1. Proposed strategy.



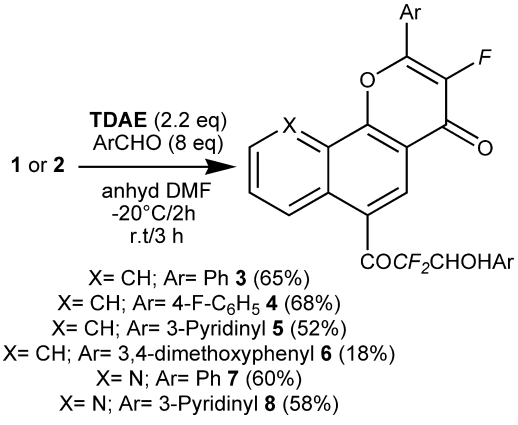
Scheme 2. Starting materials synthesis.

of this solid clearly showed two doublets of doublets centred at δ_F −106.7 and −118.7 ppm/$CFCl_3$ with $^2J_{F-F} = 272$ Hz and $^3J_{H-F} = 6.3$ and 17.7 Hz and two doublets centred at δ_F −122.4 and −122.7 ppm/$CFCl_3$ with $^2J_{H-F} \sim 55$ Hz [corresponding to the *N*,*N*-dimethyl-2,4-bis(difluoroacetyl)-1-naphthylamine], in the ratio of 8 to 2. Also two singlets were observed at δ_F −158.51 and −158.81 ppm/$CFCl_3$ in the ratio of 3 to 1. TLC analysis and proton NMR also indicated that still some PhCHO remained. Further trituration with hot cyclohexane, filtration over silica gel gave the pure 4*H*-benzo[*h*]-chromen-4-one derivative **3** in a 65% isolated yield.[19] The fluorine NMR spectrum of **3** confirmed the presence of two doublets of doublets centred at δ_F −106.04 and −117.14 ppm/$CFCl_3$ with $^2J_{F-F} = 272$ Hz and $^3J_{H-F} =$ 6.27 and 17.70 Hz and a singlet at δ_F −159.61 ppm/$CFCl_3$.

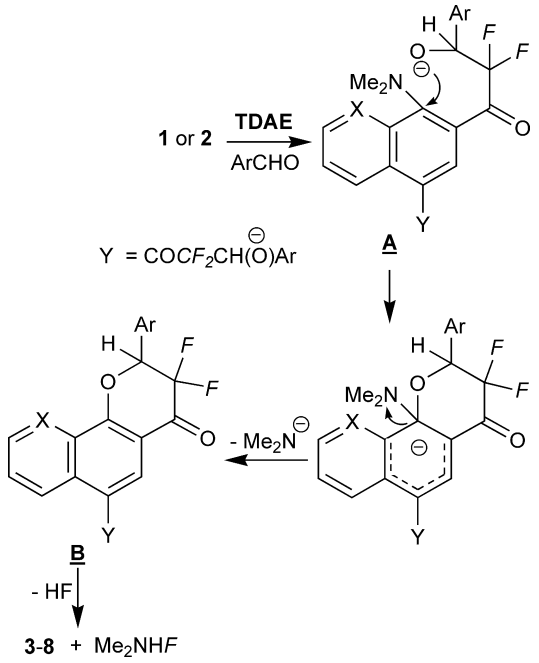
The reaction was found to be quite general when extended to other aldehydes and to substrate **2**. A series of new benzo[*h*]chromen-4-one derivatives **3**–**6** and 4*H*-pyrano[3,2-*h*]quinolin-4-one derivatives **7**,**8** were thus obtained in moderate to good yields (Scheme 3), with the exception of compound **6**, bearing a 3,4-dimethoxyphenyl moiety, obtained in a relatively low yield (18%). With this aldehyde, the major product was found to be the *N*,*N*-dimethyl-2,4-bis(difluoroacetyl)-1-naphthyl-amine in addition to other fluorinated impurities. Usually all the reactions needed less than 4 h for completion as checked by TLC and fluorine NMR. Target compounds **3**–**8** were obtained by simple trituration of the crude extract with cyclohexane and filtration over silica gel.

All the compounds have quite poor solubility in organic solvents such as $CHCl_3$, CH_2Cl_2, acetone, acetonitrile and hexane. They are *relatively* soluble in EtOAc, DMSO and MeOH.

A tentative mechanism for this reaction is depicted in Scheme 4. TDAE is able to promote the reduction of the two C–Cl bonds thus generating a bis-enolate, that can be trapped with the aldehyde (in excess) to yield the corresponding bis-alcoholate **A**; it subsequently undergoes an addition–elimination reaction yielding the difluoromethylene derivative **B** and the corresponding NMe_2 anion (N–O exchange reaction), which could act as a strong base and induces an H–F elimination, giving finally the fused derivatives **3**–**8**. Also an internal proton-transfer from the enolate may also occur.



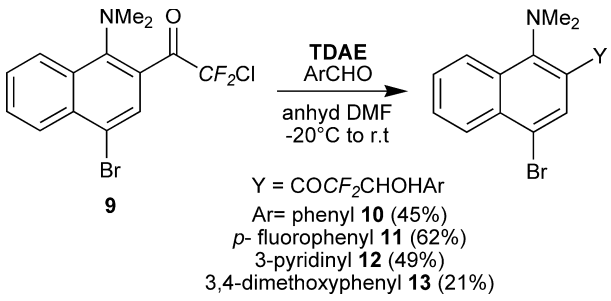
Scheme 3. TDAE mediated synthesis of fluorinated 4*H*-benzo[*h*]chromen-4-one and 4*H*-pyrano[3,2-*h*]quinolin-4-one derivatives **3**–**8**.



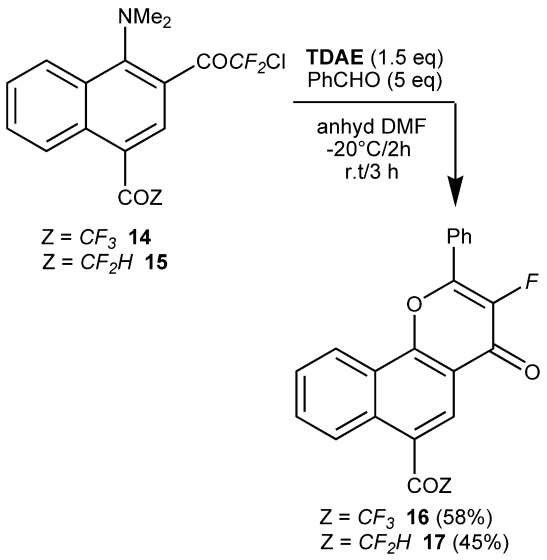
Scheme 4. Proposed mechanism.

The efficient synthesis of these new 4*H*-benzo[*h*]chromen-4-one and 4*H*-pyrano[3,2-*h*]quinolin-4-one derivatives using substrates **1** and **2**, is in sharp contrast to the TDAE mediated reduction of the *N*,*N*-dimethyl-2-chlorodifluoroacetyl-4-bromo-1-naphthylamine **9** in the presence of heteroaryl aldehydes, where the corresponding carbinol adducts were obtained in moderate to good yields, without any formation of the cyclized products (Scheme 5).[13e] Therefore the presence of two activating –$COCF_2Cl$ moieties seem to be essential for the intramolecular S_NAr cyclization.

We are currently trying to optimize some of the yields, and to extend the approach to other *ortho*-chlorodifluoroacetyl substrates, and there are preliminary results showing



Scheme 5. Previous TDAE mediated reductive addition of *N*,*N*-dimethyl-2-chlorodifluoroacetyl-4-bromo-1-naphthyl-amine **9** in the presence of aldehydes.



Scheme 6. Extension of the methodology to new substrates **14** and **15**.

that the reaction can be extended to substrates **14**–**15**, which undergo reaction with benzaldehyde under similar conditions previously described for **1** and **2** (Scheme 6). The corresponding benzo[*h*]chromen-4-one derivatives **16** and **17** were thus obtained in 58% and 45% yields. The full results for this system will be reported in due course. Extension of this useful approach to more complex fused-derivatives as well to other electrophiles is one of our next goals.

The products described in this Letter will be screened as potential anticancer and antiviral agents.

In conclusion, we have demonstrated that TDAE is an effective reducing agent that promotes, under mild conditions, the synthesis of novel fluorinated fused-heterocyclic derivatives. Although the reaction mechanism is not fully understood, a mechanistic pathway involving an SET tandem aldol/S_NAr process has been proposed.

Acknowledgements

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19. A typical procedure for the reaction between **1**, TDAE and benzaldehyde is as follows: Into a two-necked flask were added, under nitrogen at −20 °C, a 5 ml anhydrous DMF solution of **1**

(0.50 g, 1.26 mmol) and benzaldehyde (1.07 g, 10.08 mmol, 1.02 ml). The solution was stirred and maintained at this temperature for 30 min and then was added dropwise (via a syringe) the TDAE (0.51 g, 2.53 mmol, 0.59 ml). A red colour immediately developed with the formation of a white fine precipitate. The solution was vigorously stirred at −20 °C for 2 h and then warmed up to room temperature for 3 h. After this time TLC analysis (petroleum ether/EtOAc, 80:20) showed that ketone **1** was totally consumed. The brown-orange turbid solution was filtered (to remove the octamethyloxamidinium dichloride) and hydrolyzed with 50 ml of brine. A copious precipitate was formed which was extracted with EtOAc (3 × 50 ml), the combined organic extracts washed with brine (3 × 50 ml), H_2O (3 × 50 ml) and dried over Na_2SO_4. Evaporation of the solvent left an orange viscous liquid as crude product. Trituration with hot cyclohexane (to remove unreacted aldehyde) left an orange solid (0.42 g). TLC analysis (petroleum ether/EtOAc, 70:30) revealed that this solid contain one major product with some aldehyde. The solid was further triturated with hot cyclohexane, purified by filtration over silica gel (elution with petroleum ether/EtOAc, 90/10) to yield 0.31 g (0.65 mmol, 65%) of pure **3** as a yellow solid. *6-(2,2-Difluoro-3-hydroxy-3-phenylpropanoyl)-3-fluoro-2-phenyl-4H-benzo[h]-chromen-4-one*. ^{1}H NMR (DMSO-d_6/300 MHz): δ_H 5.36 (1H, dt, $J = 20.5$, 5.46 Hz, –C*H*OH), 6.91 (1H, dd, $J = 6.60$, 1.32 Hz), 7.39–7.54 (5H, m), 7.71–7.73 (3H, m), 7.91–8.00 (2H, m), 8.16–8.24 (3H, m), 8.65 (1H, d, $J = 2.07$ Hz), 8.75–8.79 (1H, m). ^{19}F NMR (DMSO-d_6/280 MHz): δ_F −106.04 (1F, dd, $J = 272.0$, 6.27 Hz), −117.14 (1F, dd, $J = 272.0$, 17.70 Hz), −159.61 (1F, s). MS (CI/CH_4): 475 (MH^+), 369 (MH^+−PhCHOH), 107 (PhCHO). HRMS (ESI): calcd for $C_{28}H_{17}F_3O_4$ 474.1079, found 474.1157. Anal. Calcd for $C_{28}H_{17}F_3O_4$: C, 70.89; H, 3.61. Found 71.20; H, 3.82.