Tetrakis(dimethylamino)ethylene (TDAE) Mediated Addition of Heterocyclic Difluoromethyl Anions to Heteroaryl Aldehydes. A Facile Synthetic Method for New *gem*-Difluorinated Alcohols Derived from 4-Bromo-1-naphthylamine and 8-Quinolylamine

Maurice Médebielle,*[a] Robert Keirouz,[a] Etsuji Okada,[b] Takuro Ashida[b]

[a]Université Claude Bernard-Lyon 1, Laboratoire de Synthèse, Electrosynthèse et Réactivité des Composés Organiques Fluorés (SERCOF), UMR CNRS 5622, Bâtiment E. Chevreul, 43 Bd du 11 Novembre 1918, F-69622 Villeurbanne Cedex, France

[b]Department of Chemical Science and Engineering, Faculty of Engineering, Kobe University, Rokkodai-cho, Nada-ku, Kobe 657-8501, Japan

Fax +33 (4) 72 43 13 23; E-mail: medebiel@univ-lyon1.fr

Received 15 March 2001

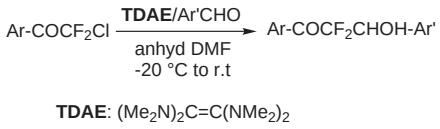
Abstract: New heterocyclic-CF_2CHOH-Ar derivatives, derived from *N*,*N*-dimethyl-4-bromo-2-difluoracetyl-1-naphthylamine and *N*,*N*-dimethyl-5-difluoroacetyl-8-quinolylamine, are easily obtained in moderate to good yields from the tetrakis(dimethylamino)ethylene (TDAE) mediated reduction of the corresponding -$COCF_2Cl$ starting materials in the presence of heteroaryl aldehydes.

Key words: electron transfer, fluorine, naphthylamines, quinolylamines, heterocycles

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] Fluorinated substituted aromatics and heterocycles, may found 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 the Alzheimer 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-naphthylamine,[8] and *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 in various fluorinated fused-heterocycles of potential biological importance. As part of our ongoing efforts in the search of new methodologies to the synthesis of fluorinated compounds with potential biological and synthetic applications,[10] we wish to present a synthetic method to prepare, under very mild conditions, new -CF_2CHOH- derivatives that incorporate quinoline as well as naphthalene units. These new difluoromethylene aromatics and heterocycles were designed for further chemical elaboration as part of a project devoted to the synthesis of new therapeutic agents.

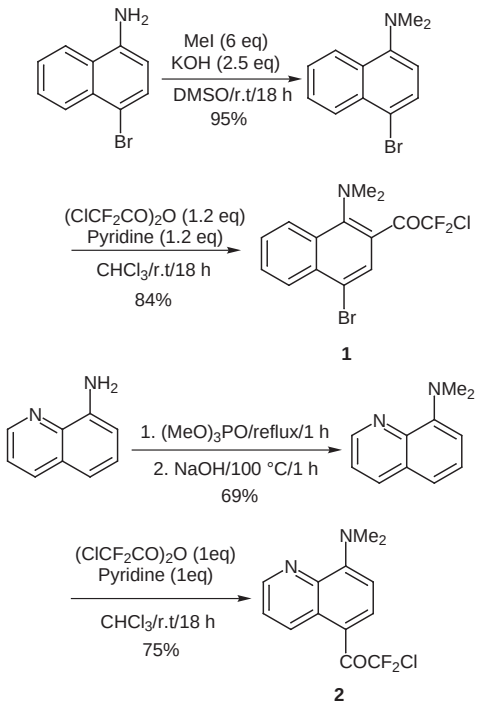
Careful examination, by cyclic voltammetry, of the reduction potential of starting materials *N*,*N*-dimethyl-4-bromo-2-chlorodifluoracetyl-1-naphthylamine **1** (Ep_{c1} = –1.20 V *vs* SCE, first peak potential measured in DMF/0.1 M NBu_4PF_6) and *N*,*N*-dimethyl-5-chlorodifluoroacetyl-8-quinolylamine **2** (Ep_{c1} = –1.14V *vs* SCE, first peak potential measured in DMF/0.1 M NBu_4PF_6), clearly shown that these -$COCF_2Cl$ substrates were good electron-acceptors and therefore prompted us to use the tetrakis(dimethylamino)ethylene (TDAE) as a mild and efficient organic reductant[11] for the in situ generation and trapping of the corresponding α,α-difluoroacetyl anions, with a series of aromatic and heterocyclic aldehydes (Scheme 1).



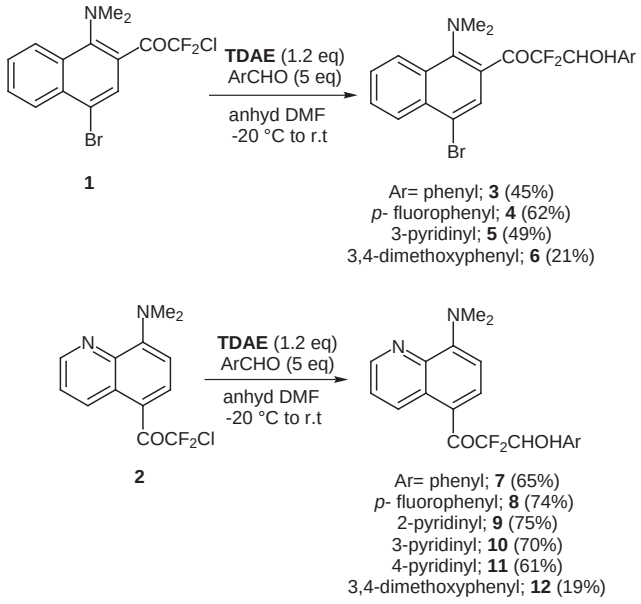
Scheme 1

Starting materials **1** and **2** were prepared in good yields in two steps, *N*,*N*-dimethylation (MeI/KOH in DMSO for **1**; trimethyl phosphate/NaOH for **2**) and subsequent 2-chlorodifluoroacetylation [chlorodifluoroacetic anhydride (CDFAA)/Pyridine in $CHCl_3$] from commercially available 4-bromo-1-naphthylamine and 8-quinolylamine (Scheme 2).

In a typical experiment, 1 equivalent of ketone **1** was condensed, in anhydrous DMF at –20 °C, with 5 equivalent of benzaldehyde in the presence of TDAE; a 1.2 equivalent of TDAE was necessary for complete reduction of the starting ketone **1**, with the reaction being almost complete after two hours (TLC monitoring). After usual work-up,



Scheme 2



Scheme 3

fluorine NMR of the crude product revealed the presence of the desired alcohol **3** characterized by two doublets of doublet (δ_F –109.1 and –118.7 ppm/$CFCl_3$ with $J_{F\text{-}F}$ = 269 Hz and $^3J_{H\text{-}F}$ = 17.42 and 6.42 Hz) and the hydrogenolysis product, the difluoroacetylated ketone (δ_F −125.7 ppm/$CFCl_3$; doublet with $^2J_{H\text{-}F}$ = 54.2 Hz) in the ratio 2 to 1. The alcohol adduct was isolated as a yellowish solid in 45% yield after purification by silica gel chromatography and recrystallization.[12] Similarly, in the presence of benzaldehyde (5 equiv) and TDAE (1 equiv), ketone **2** gave the desired alcohol **7** in 65% yield. Formation of the products was monitored by TLC and the yields were moderate to good (Scheme 3). At the end of the reaction, the corresponding insoluble $TDAE^{2+}$, $2Cl^-$ salt is recovered, demonstrating that the TDAE has been clearly oxidized. The only side-products which represent the remaining balance material were the hydrogenolysis compounds RCF_2H resulting from protonation of the difluoromethyl anions. All of the compounds were isolated as colored solids, in moderate to good yields, after purification by silica gel chromatography. With 3,4-dimethoxybenzaldehyde, formation of significant amount of fluorinated by-products was observed by fluorine NMR of the crude products; as a consequence, yields of the corresponding alcohols were quite low. These polar compounds were removed during the silica gel chromatography purification.

None of the yields have been optimized and room for improvement certainly exists.

In conclusion, we have demonstrated, that under very mild conditions, new *gem*-difluorinated heterocycles derived from quinoline and naphthalene, could be obtained in reasonable yields with the tetrakis(dimethylamino)ethylene (TDAE) as an efficient electron transfer reagent. The compounds synthesized in this work are potentially useful for biological applications. Work is under progress to extend this methodology to other halogenodifluoromethylated heterocycles of biological interest. Further chemical elaboration with these derivatives will be done in a due course.

Acknowledgement

M. M. would like to thank the CNRS for support of this work through a research grant (Aide aux Jeunes Equipes-Appel d'Offres 2000).

References and Notes

(1) Tozer, M. J.; Herpin, T. *Tetrahedron* **1996**, *52*, 8619-8683.
(2) Burger, K.; Wucherpfennig, U.; Brunner, E. *Adv. Heterocycl. Chem*. **1994**, *60*, 1. Bergstrom, D. E.; Swartling, D. J. *Fluorine Substituted Analogues of Nucleic Acid Components*, In *Fluorine-Containing Molecules, Structure, Reactivity, Synthesis and Applications*, Liebman, J. F.; Greenberg, A.; Dolbier, Jr, W. R., Eds.; VCH : New York **1988**, pp 259-308.
(3) Larsen, R. D.; Marcoux, J.-F. In *Progress in Heterocyclic Chemistry*; Gribble, G. W.; Gilchrist, T. L., Eds.; Pergamon: Oxford, UK, **2000**, Vol. 12, p 237.
(4) Raynes, K. J.; Stocks, P. A.; O'Neill, P. M.; Park, B. K.; Ward, S. A. *J. Med. Chem*. **2000**, *42*, 2747.
(5) Wilson, W. D.; Zhao, M.; Patterson, S. E.; Wydra, R. L.; Janda, L.; Strekowski, L. *Med. Chem. Res*. **1992**, *2*, 102. Strekowski, L.; Mokrosz, J. L.; Honkan, V. A.; Czarny, A.; Cegla, M. T.; Wydra, R. L.; Patterson, S. E.; Schinazi, R. F. *J. Med. Chem*. **1991**, *34*, 1739.
(6) Proctor, G. R.; Harvey, A. L. *Curr. Med. Chem.* **2000**, *7*, 295.

(7) Hojo, M.; Masuda, R.; Okada, E.; Miya, H. *Synthesis* **1989**, 870. Hojo, M.; Masuda, R.; Okada, E. *Tetrahedron Lett*. **1987**, *28*, 6199.
(8) Okada, E.; Tsukushi, N.; Otsuki, Y.; Nishiyama, S.; Fukuda, T. *Synlett* **1999**, 126.
(9) Okada, E.; Tsukushi, N.; Shimomura, N. *Synthesis* **2000**, 237. Okada, E.; Tsukushi, N. *Synlett* **1999**, 210.
(10) Fujii, S.; K. Kato, K.; Médebielle, M. *Tetrahedron* **2000**, *56*, 2655. Burkholder, C.; Dolbier, W. R.; Jr.; Médebielle, M. *J. Fluorine. Chem*. **2000**, *102*, 369-376. Burkholder, C.; Dolbier, W. R.; Jr.; Médebielle, M.; Ndedi, A. *Tetrahedron Lett.* **1998**, *39*, 8853. Burkholder, C.; Dolbier, W. R.; Jr.; Médebielle, M. *J. Org. Chem.* **1998**, *63*, 5385. Okada, E.; Tsukushi, N.; Shimomura, N. *Synthesis* **2000**, 1822. Okada, E.; Sakaemura, T.; Shimomura, N. *Chem. Lett*. **2000**, 50. Okada, E.; Tsukushi, N. *Synthesis* **2000**, 499. Okada, E.; Tsukushi, N. *Heterocycles* **2000**, *53*, 127.
(11) Burkholder, C.; Dolbier, W. R.; Jr.; Médebielle, M.; Ndedi, A. *Tetrahedron Lett.* **1998**, *39*, 8853. Burkholder, C.; Dolbier, W. R.; Jr.; Médebielle, M. *J. Org. Chem.* **1998**, *63*, 5385.
(12) A typical procedure for the reaction between **1**, **3** and TDAE is as follows: Into a three-necked flask equipped with a calcium chloride drying tube, and a nitrogen inlet was added, under nitrogen, 5 mL of anhydrous DMF and then **1** (0.50 g, 1.38 mmol) followed by **3** (0.73 g, 6.9 mmol). The solution was cooled down to –20 °C, stirred and maintained at this temperature for 30 min and then was added dropwise (via a syringe) TDAE (0.34 g, 1.66 mmol). A red color immediately developed with the formation of a white fine precipitate. The solution was vigorously stirred at –20 °C for 1 hour and then warmed up to room temperature for two hours (orange-red color). After this time TLC analysis [EtOAc/petroleum ether (85:15)] clearly showed that **1** was totally consumed. The orange-red turbid solution was filtered (to remove the octamethyloxamidinium dichloride) and hydrolyzed with 30 mL of an aqueous NaCl solution. The aqueous solution was extracted with CH_2Cl_2 (3 × 30 mL), the combined organic solutions washed with brine (3 × 30 mL), H_2O (3 × 30 mL) and dried over $MgSO_4$. Evaporation of the solvent left a red viscous liquid as crude product. Fluorine NMR shown that the desired alcohol adduct was obtained with some reduction product in a ratio 2 to 1. Purification by silica gel chromatography [EtOAc/petroleum ether (95:5)] gave 0.27 g (0.62 mmol, 45%) of **3** as a yellowish crystalline solid after recrystallization from EtOAc/petroleum ether (1/4): **1-(4-Bromo-1-dimethylamino-2-naphthyl)-2,2-difluoro-3-hydroxy-3-phenyl-propan-1-one:** Mp = 139-140 °C. ^{1}H NMR ($CDCl_3$): δ_H 2.93 (6H, s, -NMe_2), 5.38-5.48 (1H, dd, *J* = 17.3, 6.40 Hz, -C*H*OH), 7.44-7.65 (8H, m), 8.15-8.22 (2H, dd, *J* = 7.39, 6.42 Hz), ^{19}F NMR ($CDCl_3$/ $CFCl_3$): δ_F –106.96 (1F, dd, *J* = 269, 6.40 Hz), –117.62 (1F, dd, *J* = 269, 17.32 Hz). HRMS: Calcd for $C_{21}H_{18}BrF_2NO_2$ 433.0489, Found 433.0495.

Article Identifier:
1437-2096,E;2001,0,06,0821,0823,ftx,en;D06801ST.pdf