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Tetrakis(dimethylamino)ethylene (TDAE) as a Useful Reductant of Some Chlorodifluoromethylated Ketones. A New Approach for the Synthesis of α,α-Difluoroketone Derivatives.

Conrad Burkholder and William R. Dolbier, Jr

University of Florida, Department of Chemistry, P. O. Box 117200, Gainesville, FL 32611-7200, USA.

Maurice Médebielle*[$] and Alexandre Ndedi

Université Denis Diderot, Laboratoire d'Electrochimie Moléculaire associée au CNRS, 2 Place Jussieu, 75251 Paris Cedex 05, France.

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Abstract: Tetrakis(dimethylamino)ethylene (TDAE) was found to be an effective reductant of chlorodifluoromethylated ketones **1-3**. The generated α,α-difluoroacetyl anion was trapped with several aldehydes **4-7**, under mild conditions, to give the corresponding 2,2-difluoro-3-hydroxy ketone derivatives **8-13**, in moderate yields.

There continues to be an interest in the synthesis of new *gem*-difluorinated compounds because of the potential biological properties of such molecules[1]. Many selectively fluorinated analogues of biologically important compounds have experienced dramatic enhancement in their biological activity[2]. Electrophilic carbonyl derivatives, such as α,α-difluoroketones, are compounds of great interest because they have the capability to form hydrates and hemiketals[3a]. It is believed that this property allows some fluorinated ketones to mimic the transition states involved in the hydrolytic action of proteases and esterases as well as many other enzymes[3b,e]. Recently a series of α,α-difluoroketones have also shown interesting activities as HIV-1 proteases inhibitors[3b,4]. The Reformatsky reaction of halodifluoroacetates and halodifluoroketones is by far the most common method of making such bioactive compounds[5]. However, success of such reactions usually requires the use of catalysts such as zinc and catalytic titanium chloride[6], copper chloride for the reaction with aldehydes and silver acetate for ketones[5b], a catalytic amount of $CeCl_3$,[7] or Et_2AlCl with a catalytic amount of AgOAc[8]. Ultrasonic activation of a preformed organozinc reagent[9] and an electrochemical nickel catalyzed reaction with methyl chlorodifluoroacetate and a sacrificial zinc anode,[10a] and electrochemical reductive coupling reactions of methyl chlorodifluoroacetate with aldehydes using a lead cathode have also been reported[10b]. An alternative and milder methodology for generating a difluoroacetyl anion, is a goal worth pursuing.

As part of our ongoing effort in the synthesis of new fluorinated compounds with potential biological and synthetic applications[11], we wish to report the novel use of tetrakis(dimethylamino)ethylene (TDAE), as an electron donor, to generate stable α,α-difluoroacetyl anions from chlorodifluoromethylated ketones **1-3**. These

[$] FAX: +33 (0) 1. 44. 27. 76. 25. E-mail: mauricem@paris7.jussieu.fr

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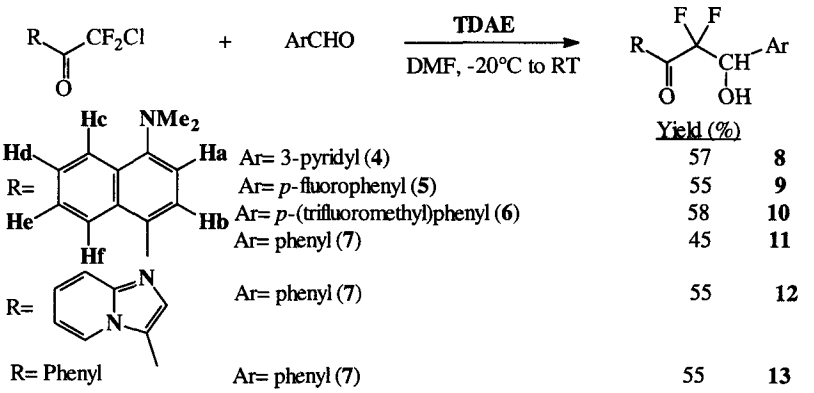
carbanions undergo in situ nucleophilic addition to aromatic aldehydes **4-7** to prepare 2,2-difluoro-3-hydroxy ketone derivatives **8-13**.



			Yield (%)	
1	R=	Ar= 3-pyridyl (**4**)	57	**8**
		Ar= *p*-fluorophenyl (**5**)	55	**9**
		Ar= *p*-(trifluoromethyl)phenyl (**6**)	58	**10**
		Ar= phenyl (**7**)	45	**11**
2	R=	Ar= phenyl (**7**)	55	**12**
3	R= Phenyl	Ar= phenyl (**7**)	55	**13**

Cyclic voltammetry of **1**[12a] (in anhydrous DMF + 0.1M Et_4NBF_4) shows that the first bielectronic wave (as compared with the one-electron oxidation wave of the ferrocene) located at -1.25V vs SCE (E_{pc1} at 0.2V/s on a glassy carbon electrode) is irreversible (up to 100V/s) and corresponds to the cleavage of the $-CF_2-Cl$ bond and to the formation of the corresponding difluoroacetyl derivative (the *N,N*-dimethyl-1-naphthylamine-4-difluoroacetyl, $RCOCF_2H$ **14**[12b]) as the reduction product as was shown by comparison with an authentic sample[12b]. The cleavage of the radical anion is very fast and therefore the major pathway of the α,α-difluoroacetyl radical is a further reduction to the hydrogenolysis product, probably at a close potential to **1**. Our studies on the cyclic voltammetry of TDAE[11a] as well as on the chlorodifluoromethylated ketones (E_{pc1}= -1.31V vs SCE for **2** and E_{pc1}=-1.15V vs SCE for **3** at 0.2V/s) at this point prompted us to try TDAE as a mild and conceptually-different synthetic electron transfer reagent, for the generation of difluoroacetyl anions, and subsequent reactions with aromatic aldehydes as trapping agents. As we have reported for the reactions involving bromodifluoromethylated heterocycles[11a, 13], an equimolar amount of TDAE was necessary for complete reduction of the starting ketones, with the reactions being almost complete after two hours. The best yields of alcohols **8-13** were obtained using a 5 molar excess of the respective aldehyde. Formation of the products was monitored by TLC and the yields were moderate. The only side-products which represent the remaining balance material were the hydrogenolysis compounds $RCOCF_2H$ resulting from protonation of the α,α-difluoroacetyl anion.

The imidazo[1,2-a]pyridine skeleton (**2**) is an important heterocycle often found in many bioactive compounds[14]; the reaction of the ketone **2**[15] with benzaldehyde (1 molar equivalent), gave after column chromatography, a mixture of the alcohol adduct **12** along the reduction product. Attempts to separate these two

products were unsuccessful. The alcohol **13** is a known compound[5]. The structures of compounds **8-13** obtained after column chromatography, were confirmed by their spectral and analytical data[16].

All of the reactions seem to involve the formation of a charge transfer complex between the starting ketones and the TDAE. Upon raising the temperature, this complex gradually decomposed to generate an α,α-difluoroacetyl anion which is apparently stable enough to react with aromatic aldehydes. In all the experiments, $[TDAE]^{2+}2Cl^-$ was recovered by simple filtration at the end of the reaction (in 60-65% yield based on the starting material) demonstrating that the TDAE has been clearly oxidized. A stepwise single electron transfer mechanism between the TDAE and the starting chlorides **1-3** should occur in all the reactions.

In conclusion, TDAE has been found to have a remarkable ability to generate stable difluoroacetyl anions from chlorodifluoromethylketones. Such a methodology should be able to be extended to other chlorodifluoromethylated ketones of biological interest. The alcohol derivatives synthesised in this work should be good candidates for further chemical elaboration,[11e] and work along this line is in progress.

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12. (a) Prepared in 75% isolated yield, by chlorodifluoroacetylation (1 molar equivalent) of the *N,N*-dimethyl-1-naphthylamine in anhydrous $CHCl_3$ in the presence of pyridine (1 molar equivalent): m.p=74°C. ^{1}H NMR ($CDCl_3$): δ_H= 3.11 (6H, s, NMe_2), 6.91 (1H, H_a, d, J=8.5Hz), 7.49-7.69 (2H, m, H_d and H_e), 8.16-8.31 (2H, m, H_c and H_f), 9.02 (1H, H_b, d, J=8.94Hz). ^{19}F NMR ($CDCl_3$/ $CFCl_3$): δ_F= -58.09 (2F, s). Anal. Calcd for $C_{14}H_{12}ClF_2NO$: C 59.36, H 4.24, N 4.94. Found C 59.10, H 4.43, N 4.76. (b) Prepared in 69% isolated yield, using sodium formaldehyde sulphoxylate (Rongalite) as the reductant, **1** as the starting ketone, in refluxing absolute ethanol for two hours: m.p= 70-72°C (yellow powder). ^{1}H NMR ($CDCl_3$): δ_H 3.07 (s, 6H, $-NMe_2$), 6.44 (t, 1H, $-CF_2H$, $2J_{H-F}$= 57Hz), 6.92 (d, 1H, H_a, J=8.36Hz), 7.50-7.68 (m, 2H, H_d and H_e), 8.13-8.20 (m, 2H, H_c and H_f), 9.2 (d, 1H, H_b, J=8.38Hz). ^{19}F NMR ($CDCl_3$/$CFCl_3$): δ_F -119.31 (d, 2F, $2J_{F-H}$=54Hz).). Anal. Calcd for $C_{14}H_{13}F_2NO$: C 67.46, H 5.22, N 5.62. Found C 67.68, H 5.43, N 5.87.

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15. Prepared in 81% isolated yield by chlorodifluoroacetylation of the imidazo[1,2-a]pyridine, in anhydrous 1,2-dichloroethane, under reflux for 2 hours: m.p= 145°C (yellow needles). ^{1}H NMR ($CDCl_3$): δ_H= 7.24-7.32 (1H, m), 7.65-7.73 (1H, m), 7.87-7.93 (1H, m), 8.61-8.63 (1H, m), 9.61-9.65 (1H, dd, J=4.6, 1.14Hz). ^{19}F NMR ($CDCl_3$/ $CFCl_3$): δ_F= -65.5 (2F, d, J=2.17Hz). Anal. Calcd for $C_9H_5ClF_2N_2O$: C 46.95, H 2.17, N 12.17. Found C 47.06, H 2.33, N 12.43.

16. A typical procedure for the reaction between **1**, TDAE and the 3-pyridine carboxaldehyde **4** 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 **1** (0.50g, 1.77 mmol) and 3-pyridine carboxaldehyde **4** (0.95g, 8.85 mmol ; 0.83 ml). The solution was stirred and maintained at this temperature for 30 min and then was added dropwise (via a syringe) the TDAE (0.35g, 1.77 mmol, 0.41 ml). 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. After this time TLC analysis (EtOAc-hexane, 90-10) clearly showed that the ketone **1** 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 $CHCl_3$ (3x30 mL), the combined organic solutions washed with brine (3x30 ml), H_2O (3x30 ml) and dried over $MgSO_4$. Evaporation of the solvent left an orange-red viscous liquid which was triturated with hot hexane (3x10 ml, to remove unreacted aldehyde) to leave an insoluble viscous orange oil. Column chromatography (EtOAc-hexane, 90-10 as eluent) and recrystallization from $CHCl_3$/hexane (1/2, v/v) gave 0.36g (1.01 mmol, 57%) of the alcohol **8**: **1-(4-dimethylamino-napthalen-2-yl)-2,2-difluoro-3-hydroxy-3-pyridin-3-yl-propan-1-one**. M.p=75-80°C. ^{1}H NMR ($CDCl_3$): δ_H= 3.04 (6H, s, $-NMe_2$), 5.46-5.58 (1H, dd, J=19.2, 4.80Hz, -C*H*OH), 6.90 (1H, H_a, d, J=8.39Hz), 7.28-7.35 (2H, m, H_d and H_e), 7.46-7.60 (2H, m, H_c and H_f), 7.90-7.94 (1H, d, J=7.86Hz), 8.14-8.8.25 (2H, m), 8.51-8.53 (1H, d, J=4.48Hz), 8.80-8.84 (1H, H_b, d, J=8.36Hz). ^{19}F NMR ($CDCl_3$/ $CFCl_3$): δ_F= -105.68 (1F, dd, J=285, 4.70Hz), -118.95 (1F, dd, J=285, 19.53Hz). Anal. Calcd for $C_{20}H_{18}F_2N_2O_2$: C 67.41, H 5.05, N 7.86. Found C 67.68, H 5.03, N 7.83.