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Reaction of the 2-(Bromodifluoromethyl)benzoxazole with Tetrakis(dimethylamino)ethylene (TDAE) in the Presence of Aldehydes. A Convenient Synthesis of 2-(Difluoromethyl)benzoxazole Alcohols.

Conrad Burkholder and William R. Dolbier, Jr

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

Maurice Médebielle*[$]

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

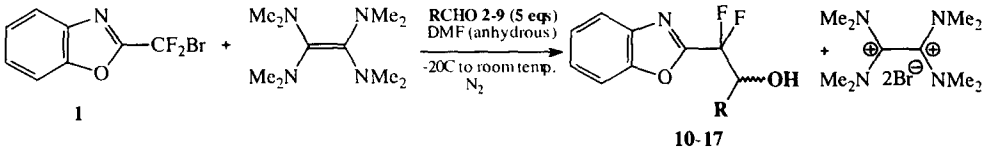
Abstract: Tetrakis(dimethylamino)ethylene (TDAE) was found to be an effective reductant of the 2-(bromodifluoromethyl)benzoxazole **1**. The generated 2-(difluoromethyl) benzoxazole anion was trapped with several aldehydes **2-9**, under mild conditions, to give the corresponding 2-(difluoromethyl)benzoxazole alcohols **10-17**, in moderate to good yields. © 1997, Published by Elsevier Science Ltd. All rights reserved.

There is an increasing interest in organofluorine chemistry for the synthesis of new *gem*-difluorinated compounds in view of the potential biological properties of such molecules[1]. Many selectively fluorinated analogues of biologically important compounds have demonstrated dramatic enhancement in their biological activity[2]. Very recently, highly desirable new methodologies for the synthesis of interesting *gem*-difluoromethylene compounds, using free-radical difluoromethylene radicals[3] as well as new nucleophilic difluoromethylene synthons[4], have been published. Tetrakis(dimethylamino)ethylene (TDAE) has an ionization potential of 6.13eV[5] and has a reducing power close to zinc[5]; in CH_3CN electrochemical oxidation of TDAE occurs in two reversible one-electron oxidation steps, to $[TDAE]^{\cdot+}$ and $[TDAE]^{2+}$at -0.78V and -0.61V vs SCE (normal potential standards, E°)[6a]. However in DMF, a two-electron reversible wave is observed at a potential close to -0.62V vs SCE[6b] (normal potential standard, E°). There are a limited number of reports on the use of TDAE in organofluorine synthesis; Pawelke et al. [7a] have first demonstrated that at low temperatures, TDAE and CF_3I form a charge transfer complex which can act as a nucleophilic trifluoromethylating agent in polar solvents; in such a way some trifluoromethyl-boron and silicon compounds were obtained in reasonable yields; later the methodology was extended to the synthesis of N-trifluoromethyl-dialkylamines through the reduction of CF_2Br_2 in the presence of secondary amines[7b]. Very recently Chambers et al. [8a] elegantly demonstrated that TDAE could act as a useful defluorination reagent of fluorinated alkenes, to yield a fluoride salt $[TDAE]^{2+}2F^-$

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

that is soluble in a wide range of organic solvents. In addition stable fluorinated anions of TDAE have been isolated using this process[8b]. Finally TDAE can react with anhydrous unsaturated fluorocarbons to produce 'in situ', powerful fluoride-ion sources. These fluoride anions were used for oligomerisation and polyfluoroalkylation reactions[8c].

Herein, we wish to report a novel utility of the tetrakis(dimethylamino)ethylene (TDAE), as an electron donor, for the generation of a stable 2-(difluoromethyl)benzoxazole anion and for the synthesis of new 2-(difluoromethyl)benzoxazole alcohols **10-17**, by the reaction of the 2-(bromodifluoromethyl)benzoxazole **1** and several aromatic aldehydes **2-9**:



1 **10-17**

Cyclic voltammetry of **1**[9] (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 -1.36V vs SCE (Ep at 0.2V/s on a glassy carbon electrode) is irreversible (up to 100V/s) and corresponds to the cleavage of the -CF_2-Br bond and to the formation of the 2-(difluoromethyl)benzoxazole as the reduction product. The other wave located at a more negative potential (Ep= -2.12V vs SCE at 0.2V/s) is attributed to the reduction of this compound as was shown by comparison with an authentic sample[9]. The cleavage of the radical anion is very fast and therefore the major pathway of the α,α-difluoroalkyl radical is a further reduction to the hydrogenolysis product, probably at a close potential to **1**. Attempts to generate the 2-(difluoromethyl)benzoxazole anion from exchange with n-BuLi in THF at -78C, resulted only in decomposition of the 2-(difluoromethyl)benzoxazole lithium derivative; therefore, use of the milder reagent, TDAE, was attempted. Initially, 0.25 equiv of TDAE and 1 equiv of **1** were mixed together for one hour in anhydrous DMF at -20°C and a deep red color immediatly developed, probably due to the formation of a charge transfer complex (as already observed in previous studies[7,8]). The solution (which slowly became orange) was warmed up to room temperature and after one hour at this temperature, was filtered (to remove the $[TDAE]^{2+}2Br^-$), hydrolyzed and worked-up. ^{19}F NMR analysis of the crude product clearly showed the formation of the the 2-(difluoromethyl)benzoxazole in 45% yield with 50% of unreacted starting material. Obviously the generation of the 2-(difluoromethyl)benzoxazole anion had been successful; subsequent experiments demonstrated that an equimolar amount of TDAE was necessary for the complete reduction of the starting bromide **1** and that the reaction was almost complete after one hour (as checked by TLC). Under these conditions, the 2-(difluoromethyl)benzoxazole was obtained in 89% yield (^{19}F NMR). Next, the 2-(difluoromethyl)benzoxazole anion was shown to be efficiently trapped by a series of aromatic aldehydes **2-9**; the best yields of the corresponding alcohols **10-17** were obtained with a 5 molar

excess of the aldehyde. Formation of the products was monitored by TLC and the yields were moderate to good (entries 1-8, table 1). A lower yield (25%) was obtained with an electron-rich donating aldehyde, the N-methyl-2-carboxaldehyde pyrrole **8** (entry 8). The structures of compounds **10-17** obtained after column chromatography, were confirmed by their spectral and analytical data[10].

Table 1: Synthesis of alcohols from the 2-(bromodifluoromethyl)benzoxazole

Entry[a]	Aldehyde	Product (%)[b]
1	Benzaldehyde **2**	**10** (62)
2	3-pyridine carboxaldehyde **3**	**11** (57)
3	2-furfural **4**	**12** (57)
4	4-fluoro benzaldehyde **5**	**13** (67)
5	α,α,α-trifluoro-p-tolualdehyde **6**	**14** (63)
6	p-cyano benzaldehyde **7**	**15** (61)
7	4-biphenyl carboxaldehyde **8**	**16** (45)
8	N-methyl-2- carboxaldehyde pyrrole **9**	**17** (25)

a: C_{sub}= 1.20×10^{-3} mol + C_{TDAE}= 1.20×10^{-3} mol + $C_{aldehyde}$= 6.0×10^{-3} mol in 10 mL of anhydrous DMF; under nitrogen. b: isolated yields.

All of the reactions seem to involve the formation of a charge transfer complex between **1** and the TDAE. Upon raising the temperature, this complex gradually decomposed to generate the 2-(difluoromethyl)benzoxazole anion which is apparently stable enough to react with aromatic aldehydes. In all the experiments, $[TDAE]^{2+}2Br^-$ was recovered by simple filtration at the end of the reaction (in 60-65% yield based on **1**) demonstrating that the TDAE has been clearly oxidized. A stepwise single electron transfer mechanism between the TDAE and the starting bromide **1** can not been ruled out and it is possible that the 2-(difluoromethyl)benzoxazole radical is an intermediate in this reaction. We have no indication of its reduction potential in DMF, but it is reasonable, in view of the cyclic voltammetric experiments, that this value would be very close to the reduction potential of **1** (Ep= -1.36V vs SCE). Therefore the 2-(difluoromethyl)benzoxazole radical could be favorably reduced by the $[TDAE]^{\cdot+}$ species. Further experiments are underway to elucidate the reaction mechanism.

TDAE has the remarkable potential to generate a stable difluoromethyl anion; the methodology should be able to be extended to other fluorinated halides. The present procedure may be utilized as a facile and convenient synthetic method for the synthesis of new *gem*-difluorinated alcohols. The present reaction should be able to be extended to other aldehydes of biological interest. We are now exploring the TDAE methodology,

presented in this letter, with other electrophiles as well as with other bromo-difluoromethylated heterocycles. The different *gem*-difluorinated alcohols synthesized in this work are also expected to be good substrates for further chemical modifications.

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10. A typical procedure for the reaction between **1**, TDAE and the 3-pyridine carboxaldehyde **3** 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 10 mL anhydrous DMF solution of **1** (0.30g, 1.20 mmol) and 3-pyridine carboxaldehyde **3** (0.64g, 6 mmol). The solution was stirred and maintained at this temperature for 30 mins and then was added dropwise (via a syringue) the TDAE (0.24g, 1.20 mmol, 280 µL). A red color immediatly 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 one hour. After this time TLC analysis (Et_2O-hexane, 90-10) clearly showed that the bromide **1** was totally consummed. The orange-red turbid solution was filtered [to remove the octamethyloxamidinium dibromide, 0.26g (0.73 mmol), 65% based on **1**], 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. Recrystallization from Et_2O gave 0.19g (0.68 mmol, 57%) of the alcohol **11**: **β,β-difluoro-α-(3-pyridyl)-2-benzoxazole ethanol**. m.p=142°C (cream powder). TLC (Et_2O): R_F= 0.50. ^1H NMR ($CDCl_3$): δ_H= 5.47-5.57 (1H, dd, J=16.9, 5.6Hz), 5.70 (1H, brs, OH), 7.28-7.93 (6H, m), 8.50 (1H, d), 8.60 (1H, s). ^{19}F NMR ($CDCl_3$/$CFCl_3$): δ_F= -107.9 (1F, dd, J_{F-F}= 281Hz, $^3J_{F-H}$= 5.2Hz), -119.6 (1F, dd, J_{F-F}= 281Hz, $^3J_{F-H}$= 16.9Hz). Mass (CI/CH_4): m/e: 277 ($M + H^+$). Analysis: Calcd. C 60.87, H 3.62, N 10.14. Found C 61.02, H 3.83, N 10.18.

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