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Review

Synthesis and reactivity of halogeno-difluoromethyl aromatics and heterocycles Application to the synthesis of *gem*-difluorinated bioactive compounds

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Abstract

In an effort to prepare new fluorine-containing compounds which are active against HIV, and based on the electrochemical reduction of a series of bromodifluoromethyl compounds, the tetrakis(dimethylamino)ethylene (TDAE) was found to be an effective reductant of the 2-(bromodifluoromethyl)benzoxazole **1** and of the 5-(bromodifluoromethyl)-3-phenyl-1,2,4-oxadiazole **3**. A stepwise electron transfer with a difluoromethyl radical as intermediate is assumed to take place in this reaction. Under mild conditions, the generated difluoromethyl heterocyclic anion was efficiently trapped with aromatic and heterocyclic aldehydes **7**–**14** and ketones **15**–**16**. In this way the corresponding β,β-difluoro-α-heteroarylated alcohols **17**–**32** were obtained in moderate to good yields. The same methodology was successfully applied to the reduction of chlorodifluoromethylated ketones **4**–**6** and the generated α,α-difluoroacetyl anion was trapped with several aldehydes **7**, **8**, **10**, **11**, under mild conditions, to give the corresponding 2,2-difluoro-3-hydroxy ketone derivatives **33**–**38**, in moderate yields. The $S_{RN}1$ reactions of 2-(bromodifluoromethyl)benzoxazole (**1**) with the anions of heterocyclic thiols and phenolic compounds were also carried out. The products **39**–**54**, which all have a CF_2 group, were tested for activity against HIV, and several were found to be active, including **44** which was very active.

Keywords: $S_{RN}1$ reactions; Electrochemistry; Bromodifluoromethyl heterocycles; Tetrakis(dimethylamino)ethylene; Chlorodifluoromethyl ketones; *gem*-Difluorinated compounds

1. Introduction

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 analogs of biologically important compounds have exhibited 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 [3–7] as well as new nucleophilic difluoromethylene synthons [8] have been published.

Trifluoromethyl-substituted heterocycles have received considerable interest because of their potential biological properties, and a large number of such heterocycles have been synthesized during the last decade [9]. However, there are few reports on the synthesis of halodifluoromethyl heterocycles [10–15], and as far as we know there exists no general method to prepare them. Such halodifluoromethyl heterocycles would be very useful starting materials to build new difluorinated heterocycles as it is anticipated that the carbon–halogen bond should be quite reactive in single electron transfer (SET) reactions, both chemically and electrochemically.

As part of our ongoing efforts in the synthesis of new fluorinated compounds with potential biological and

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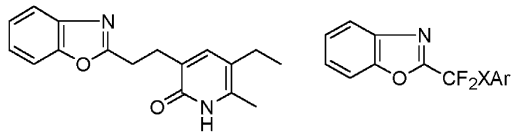


Scheme 1.

synthetic applications [16–25], we wish to report a novel use of tetrakis(dimethylamino)ethylene (TDAE), as an electron donor, to generate stable difluoromethyl heterocyclic anions [26–28], which can be utilized to react with various aldehydes and ketones in the synthesis of new β,β-difluoro-α-heteroarylated alcohols. The major objective of this work was to prepare a large spectrum of compounds for biological screening against HIV-1. However, this quest also led to the discovery of a new, general method for the in situ preparation of heteroaromatic difluoromethyl anions, which can participate in predictable reactions which have considerable synthetic utility. $S_{RN}1$ reactions involving heterocyclic and aromatic thiols and phenolates as nucleophiles were also designed in order to have access to other type of difluoromethylene derivatives [29].

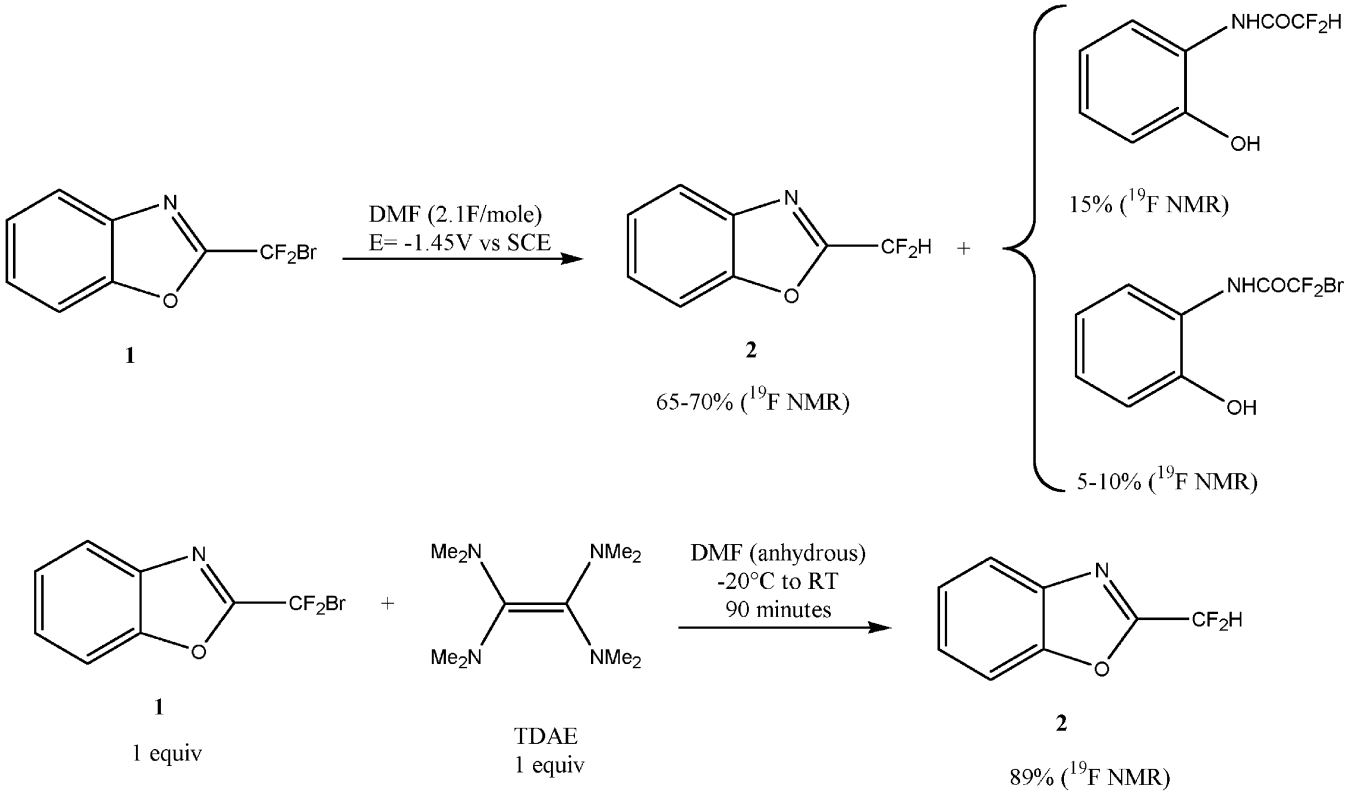
In this research, it was decided to investigate the selective substitution of fluorine into compounds similar to **A**, which is known to be a potent NNRTI [30]. Dramatic enhancements of activity have been reported in many cases for partially fluorinated analogs of biologically active compounds [2]. It was then decided to develop a synthetic method by which various analogs of **A** could be prepared where one CH_2 is replaced with a CF_2 and, for ease of synthesis, where the other CH_2 is replaced with a CHOH and heteroatom moieties (X). Thus, the plan was to keep the benzoxazole ring of **1** and modify not only the two atom tether, but the pyrimidinone ring as well, so that the target compounds would have the general appearance of **B** (Scheme 1).

2. Chemical results and discussion

Cyclic voltammetry of 2-(bromodifluoromethyl)benzoxazole **1** [31] (in anhydrous DMF + 0.1 M Et_4NBF_4) shows two successive reduction waves; the first one is irreversible (up to 500 V/s), corresponding to the uptake of 1.5 electrons (as compared with the one-electron oxidation wave of the ferrocene) and located at −1.36 V versus SCE (E_p = peak potential at 0.2 V/s on a glassy carbon electrode). This reduction step corresponds to the cleavage of the C–Br bond and to the formation of the 2-(difluoromethyl)benzoxazole **2** as the reduction product. The other irreversible wave, located at a more negative potential ($E_p = -2.12$ V versus SCE at 0.2 V/s) is attributed to the reduction of this compound as was shown by comparison with an authentic sample [31]. As expected, the 2-(chlorodifluoromethyl)benzoxazole [31] was found to be irreversibly reduced at a more negative potential than **1**, close to −1.66 V versus SCE (E_p at 0.2 V/s on a glassy carbon electrode). Bromodifluoromethyl oxadiazole compounds [31] were found to be reduced at more positive potential than the benzoxazole derivative, for example, the compound **3** is irreversibly reduced (in anhydrous DMF + 0.1 M Et_4NBF_4) at −1.20 V versus SCE (E_p at 0.2 V/s on a glassy carbon electrode) followed by a small irreversible wave located at a more negative potential close to −2.0 V versus SCE.

Preparative electrolysis of **1** ($C = 5.74$ mM in anhydrous DMF + 0.1 M Et_4NBF_4) at −1.45 V versus SCE on a carbon felt cathode, gave after the consumption of 2.1 F/mol the 2-(difluoromethyl)benzoxazole **2** in 65–70% yield (^{19}F NMR); the side products which represent the remaining balance material were the *N*-(2-hydroxy difluoromethyl) amide (15%, ^{19}F NMR) and the *N*-(2-hydroxy bromodifluoromethyl) amide (5–10%, ^{19}F NMR) resulting from the hydrolysis of the starting material and of the reduction product (Scheme 2).

Then the question was posed: could we generate a stable and reactive difluoromethyl heterocyclic anion, chemically and/or electrochemically that could be used in synthetic reactions? The preparative electrolysis of **1** in the absence of any electrophile, indicated that indeed the difluoromethyl anion had been produced. However, a preparative electrolysis of **1** ($C = 5.74$ mM in anhydrous DMF + 0.1 M Et_4NBF_4) in the presence of an excess of **7** ($C = 28.7$ mM) as trapping agent, at −1.45 V versus SCE on a carbon felt cathode, gave as major product only **2** ($Y = 65\%$ by ^{19}F NMR), with only traces of the alcohol **17** ($Y = 10\%$ by ^{19}F NMR). Apparently the difluoromethyl anion, under those conditions, is not sufficiently reactive to react efficiently with benzaldehyde. Subsequent attempts to generate the 2-(difluoromethyl)benzoxazole anion via exchange with *n*-BuLi in THF at −78°C, resulted only in decomposition of the 2-(difluoromethyl)benzoxazole lithium derivative. Attempts to form an organozinc intermediate from **1** using activated zinc in anhydrous DMF, at room temperature or at 70°C, resulted only in low conversion and minor amount of **2** (as checked by ^{19}F NMR), the major isolated material being the unreacted starting material with some formation of amides. Our studies on the cyclic voltammetry of TDAE [26–28] as well as on the bromodifluoromethyl heterocycles [26–28] at this point prompted us to try the TDAE as a milder and conceptually different synthetic electron transfer reagent. Initially, 0.25 equivalent of TDAE and 1 equivalent of **1** were mixed together for 1 h in anhydrous DMF at −20°C and a deep red color immediately developed, probably due to the formation of a charge transfer complex (as already observed in previous studies [32–35]). The solution (which slowly became orange) was warmed to room temperature and after 1 h 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 **2**, with only 50% conversion and no trace of amides. Obviously the generation



Scheme 2.

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 90 min (as checked by TLC; silica gel; hexane 80–EtOAc 20). Under these conditions, **2** was obtained in 89% yield (^{19}F NMR, Scheme 2). Under the same conditions the 2-(chlorodifluoromethyl)benzoxazole was not reduced by TDAE, even after a longer reaction time.

Next, it was demonstrated that the 2-(difluoromethyl)-benzoxazole as well as the 5-(difluoromethyl)-3-phenyl-1,2,4-oxadiazole anions could be efficiently trapped by a series of aromatic aldehydes **7–14**, and ketones **15–16**. Optimization experiments showed that the best yields of the corresponding alcohols **17–32** were obtained with a 4–5 mol excess of the electrophile. Formation of the products was monitored by TLC (hexane–EtOAc) and the yields were moderate to good (Scheme 3).

All the reactions are completed in 1–2 h as determined by TLC (hexane–EtOAc). The reactions of **1** and **3** with **8** have been conducted on a larger scale (5–10 g) and it was found that the yields were similar to those obtained on a smaller scale. Usually the reactions with the oxadiazole derivative **3** are complete in less than 2 h. Most of the β,β-difluoro-α-heteroarylated alcohols were isolated after column chromatography or by simple titration of the crude product with hexane and recrystallization. The reactions with ketones **15** and **16** gave the corresponding alcohols, albeit in modest yields, after column chromatography. The rather low yields obtained with these ketones could be explained by steric hindrance of the benzoxazole ring.

The alcohol **25** was characterized by a typical AB quartet with a fluorine–fluorine coupling constant close to 276 Hz. The addition of the 2-(difluoromethyl)benzoxazole anion to **16** gave the corresponding alcohol **26** as a single isomer characterized by a singlet ($\delta_F = -117.4$ ppm/$CFCl_3$) in its ^{19}F NMR spectrum. With the alcohols obtained in this work, a possible intramolecular H-bonding between the hydrogen of the hydroxy group and the nitrogen of the benzoxazole (N-3) or the oxadiazole (N-4) rings could be anticipated [36]. In all of the reactions, the balance of the non-adduct product mixture is **2**, as confirmed by ^{19}F NMR and TLC of the crude reaction.

All of the reactions appear to proceed via the formation of a charge transfer complex (deep red color) between **1** and **3** and the TDAE, at low temperature (−20°C). Upon raising the temperature, the solution gradually becomes orange and the complex gradually decomposes to generate the 2-(difluoromethyl)heterocyclic anion (and the $[TDAE]^{2+}$), and the putative anion is apparently stable enough to react with aromatic aldehydes and ketones. In all of the experiments, $[TDAE]^{2+}2Br^-$ was recovered by simple filtration at the end of the reaction (in 60–65% yield based on **1** or **3**) demonstrating that the TDAE has been clearly oxidized. A stepwise SET mechanism between the TDAE and the

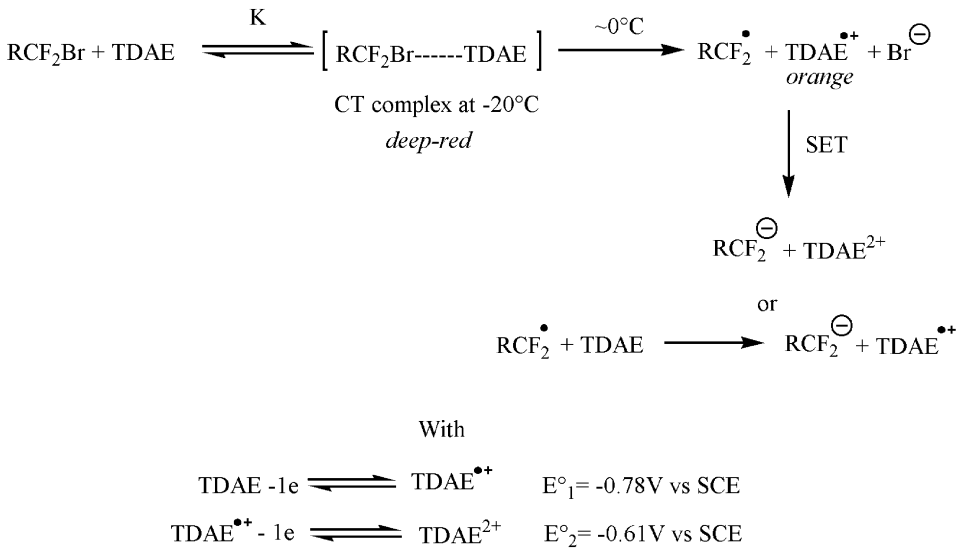
$R\text{-}CF_2Br$	ArCOR	TDAE, DMF, -20°C to RT	$R\text{-}CF_2\text{-}C(R)OH\text{-}Ar$
1 R= benzoxazole	Ar= phenyl, R=H (**7**)		**17** 62%
	Ar= 3-pyridyl, R=H (**8**)		**18** 57%
	Ar= 2-pyridyl, R=H (**9**)		**19** 55%
	Ar= p-fluorophenyl, R=H (**10**)		**20** 67%
	Ar= p-(trifluoromethyl)phenyl, R=H (**11**)		**21** 63%
	Ar= p-cyanophenyl, R=H (**12**)		**22** 61%
	Ar= biphenyl, R=H (**13**)		**23** 48%
	Ar= 2-furyl, R=H (**14**)		**24** 57%
	Ar= phenyl, R=Me (**15**)		**25** 33%
	Ar= R=-$(CH_2)_5$-(**16**)		**26** 35%
3 R= 1,2,4-oxadiazole-5-phenyl	Ar= 3-pyridyl, R=H (**8**)		**27** 62%
	Ar= 2-pyridyl, R=H (**9**)		**28** 60%
	Ar= p-fluorophenyl, R=H (**10**)		**29** 61%
	Ar= p-(trifluoromethyl)phenyl, R=H (**11**)		**30** 57%
	Ar= p-cyanophenyl, R=H (**12**)		**31** 57%
	Ar= biphenyl, R=H (**13**)		**32** 62%

Scheme 3.

starting bromides **1** or **3** should occur in all the reactions (Scheme 4).

The methodology was extended to generate stable α,α-difluoroacetyl anions from chlorodifluoromethylated ketones **4**–**6**. This approach is found to be milder compared to the classical Reformatsky reaction where activated zinc with added catalysts is often needed. These carbanions undergo in situ nucleophilic addition to aromatic aldehydes **7**, **8**, **10**, **11** to prepare 2,2-difluoro-3-hydroxy ketone derivatives **33**–**38** (Scheme 5).

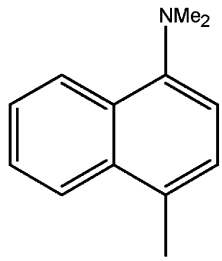
In order to prepare more compounds with structure **B**, it was expected the CF_2Br group of **1** would be reactive with sulfur nucleophiles [37]. Initial experimentation with **1** and sodium benzenethiolate leads to the observation that the reaction giving **39** was rapid and exothermic, being complete in only 15 min. It was soon discovered that a wide

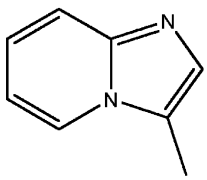


Scheme 4.

range of anions from mercapto-substituted heterocycles, RSH, was able to successfully react with **1** to give **39–48**, as can be seen by looking at Table 1. The anions were conveniently generated using dry NaH, which was weighed out rapidly in the air and transferred to the reaction apparatus as quickly as possible (Scheme 6).

The isolated yields of these reactions vary from 51 to 86%, and no significant optimization of the yields was performed other than using a two-fold excess of the anion and following the reaction by TLC until the starting material (**1**) was gone. By looking at Table 1, it can be seen that substitution of an aromatic CH with a nitrogen leads to lowered reactivity with **1**. Thus, the anion of 2-mercapto-pyridine (entry 2) is much less reactive than benzenethiolate (entry 1). Multiple nitrogen substitution in the heterocyclic ring of the anion results in greatly reduced reactivity as can be seen for the anion of 5-mercapto-1-methyltetrazole, which only reacted at 100°C after 24 h (entry 10). This is consistent with an electronic effect where electron-withdrawing substitution of the anion slows down the reaction.

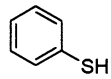
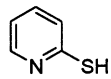
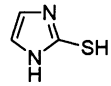
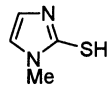
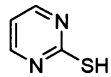
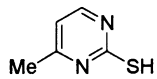
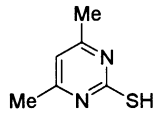
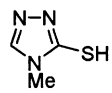
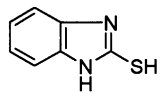
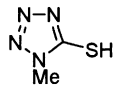




			Yield (%)	
4	R=	Ar= phenyl (**7**)	57	**36**
		Ar= 3-pyridyl (**8**)	55	**37**
		Ar= p-fluorophenyl (**10**)	58	**38**
		Ar=p-(trifluoromethyl)phenyl (**11**)	45	**35**
5	R=	Ar= phenyl (**7**)	55	**39**
6	R= Phenyl	Ar= phenyl (**7**)	55	**40**

Scheme 5.

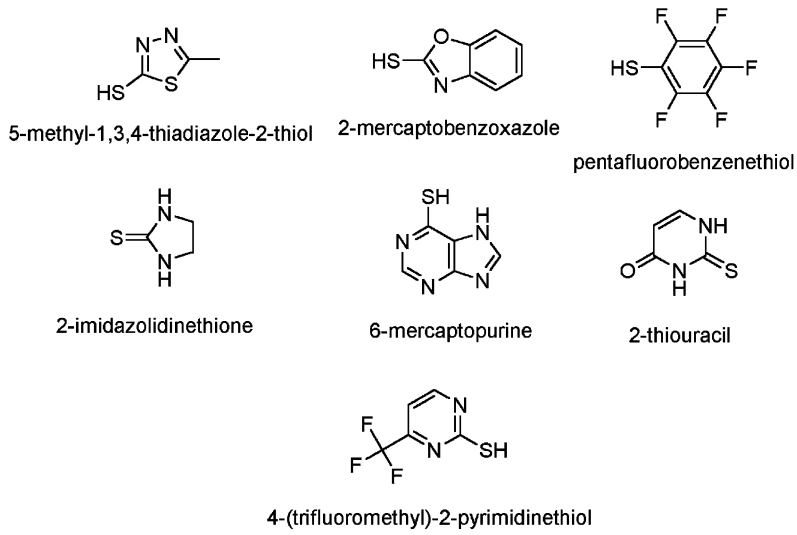
Table 1
Conditions and isolated yields for the reactions of **1** with the anions of benzenethiol and mercapto-substituted heterocycles (RSH) to give **39–48**

Entry	RSH	Conditions	Product	Yield (%)
1		RT, 15 min	**39**	86
2		RT, 23 h	**40**	82
3		RT, 23 h	**41**	51
4		RT, 23 h	**42**	76
5		60°C, 24 h	**43**	65
6		60°C, 24 h	**44**	62
7		60°C, 24 h	**45**	74
8		60°C, 24 h	**46**	72
9		60°C, 24 h	**47**	59
10		100°C, 23 h	**48**	84

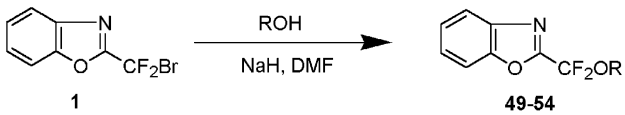
Several sulfur-based nucleophiles that did not work in this reaction were discovered, for example, the anions of 5-methyl-1,3,4-thiadiazole-2-thiol, 2-imidazolidinethione, 2-mercaptobenzoxazole, 6-mercaptopurine, pentafluorobenzenethiol, 2-thiouracil, and 4-(trifluoromethyl)-2-pyrimidinethiol (Scheme 7) gave decomposition from which none of the desired product could be isolated. Also, the attempted reaction of sodium thiocyanate leads to decomposition.

The displacement of bromide from the CF_2Br group does not occur by a simple S_N2 mechanism due to the presence of the alpha fluorines. Instead, it proceeds by an $S_{RN}1$ mechanism [38] involving a SET chain process. The observation that the presence of 1,4-dinitrobenzene strongly inhibits the reaction of **1** with sodium benzenethiolate is evidence for the $S_{RN}1$ mechanism. Thus, the reaction of the CF_2Br group is limited to nucleophiles that can react by such an $S_{RN}1$ mechanism.

Scheme 6.



Scheme 7.

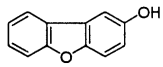
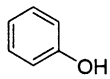
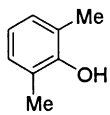
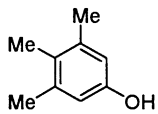
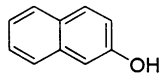
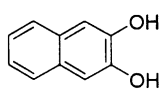


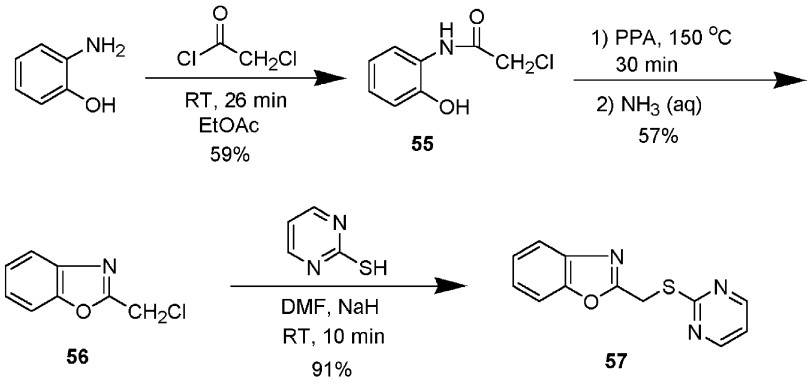
Scheme 8.

It was found that sodium phenolate reacts with the CF_2Br of **1** much more slowly than sodium benzenethiolate; however, after 24 h at room temperature, the reaction was complete, and the desired product **49** was isolated in 70% yield. In fact, other substituted phenolates, as well as related benzenoid derivatives reacted with **1** to give the expected displacement products **49–54** (Scheme 8, Table 2). The only heterocyclic oxyanion that was tried for this reaction was the anion of 2-hydroxypyridine, and it gave only decomposition when heated with **1**.

In order to be able to determine whether the fluorine substitution enhances the activity against HIV, it was necessary to prepare at least one analog of an active compound where the only difference in the chemical structure is the replacement of the two fluorine atoms with two hydrogen atoms. The active compound that was chosen for this study was **43**, and the hydrogen-substituted analog **57** was easily synthesized in three steps (Scheme 9).

Table 2
Conditions and isolated yields for the reactions of **1** with the anions of phenol and hydroxybenzenoid compounds to give products **49–54**

Entry	ROH	Conditions	Product	Yield (%)
1		RT, 6 h	**49**	44
2		RT, 24 h	**50**	70
3		RT, 24 h	**51**	32
4		RT, 24 h	**52**	47
5		RT, 24 h	**53**	42
6		100°C, 2 h	**54**	28



Scheme 9.

3. Biological activity

Compounds **17–32**, **39–54**, and **57** were evaluated in the preliminary screen of the in vitro Anti-AIDS Drug Discovery Program at the National Cancer Institute [39]. The activity data are reported as effective concentration (EC_{50}), the concentration of compound for which there is 50% protection in cells infected by HIV-1. The data for the active compounds are presented in Table 3 (all compounds not in the table were found to be inactive). The compounds are listed in order of decreasing activity, and it should be noted that smaller values for the EC_{50} are an indication of higher activity.

There are several points that are worth considering concerning the structure activity relationships in this series of compounds. Firstly, all of the active compounds were derivatives of benzoxazole, since the benzoxazole ring was retained in all the compounds synthesized for this study.

Table 3
Effective concentrations (EC_{50}) of active compounds against HIV-1

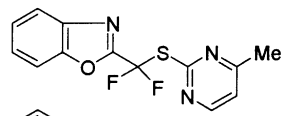
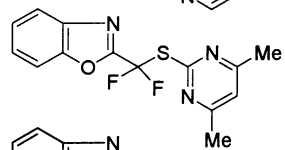
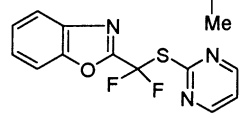
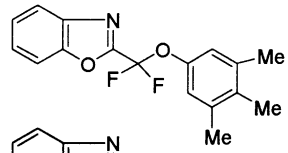
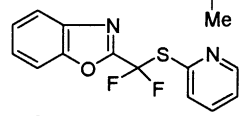
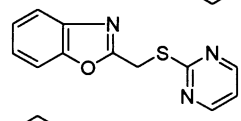
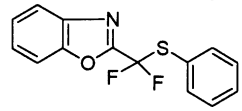
Entry	Number	Structure	$EC_{50} \times 10^{-6}$ M
1	**44**		0.0646
2	**45**		2.16
3	**43**		3.14
4	**52**		13.0
5	**40**		29.2
6	**57**		35.3
7	**39**		36.0

Table 4
Effective concentrations (EC_{50}) for **43** and **44** against drug-resistant mutant strains of HIV

Entry	Strain	$EC_{50} \times 10^{-6}$ M	
		43	**44**
1	HIV-1 (III B)	3.36	0.067
2	ddI	Inactive	0.159
3	4 × AZT (AZT-R)	0.373	Inactive
4	OC/100	4.08	0.38
5	HEPT/236	8.64	0.11
6	Calo	3.2	0.43
7	Diphenyl sulfone	Inactive	Inactive
8	HIV-2 (ROD)	Inactive	Inactive
9	SIV (B670)	Inactive	Inactive

Secondly, only compounds with six-membered rings such as benzene, pyridine, or pyrimidine rings attached to the sulfur were active, while compounds with five-membered rings such as **41**, **42**, **46–48** were inactive. Of the compounds with six-membered rings, it was found that the pyrimidine ring was most active, followed by the pyridine ring, and then the benzene ring. This conclusion follows by comparing the activities of compounds **43** (entry 3), **40** (entry 5), and **39** (entry 7). Furthermore, the activity of the pyrimidine-substituted compound is greatly enhanced by the addition of a methyl group in the four-positon of the pyrimidine ring as in **44** (entry 1), which was the most active compound in this study. The addition of a second methyl produced a decrease in the activity. Nearly all of the active compounds had a sulfur atom in the tether connecting the two heterocyclic rings, while compounds with an oxygen in place of the sulfur were all inactive except for **52** (entry 4). From comparing the activity of **39** (entry 7) to **50** which was inactive, it can be concluded that having a sulfur in the tether rather than an oxygen, enhances the activity. Lastly, but most importantly, a comparison of the activity of the fluorine-containing compound **43** (entry 3), to the hydrogen-substituted analog **57** (entry 6), leads to the conclusion that fluorine substitution is responsible for a 10-fold increase in activity. It is interesting to speculate why this may be so. The fluorine atoms may enhance the lipophilicity of the adjacent benzoxazole ring, thus, increasing its binding to the lipophilic pocket of the binding site of the reverse transcriptase enzyme. If this is the case, then it may well be that this enhancement of activity by fluorine substitution, could be applicable to many other biologically active compounds where it is possible to replace a CH_2 group which is adjacent to an aromatic ring with a CF_2 group.

Compounds **43** and **44** were referred for testing in the advanced screens, and the results can be seen by looking at Table 4. Although, the activity of **44** against the wild type HIV-1 (III B) was very good (entry 1), it was inactive against a number of mutant strains of HIV (entries 3, 7, 8, and 9). Compound **43** was similarly inactive in a number of cases (entries 2, 7, 8, and 9).

Although, the results of these studies have demonstrated that fluorine atom substitution can enhance the activity against HIV substantially, it must be concluded from the advanced screening that there is no unusual activity against drug resistant mutant strains of HIV induced by fluorine atom substitution. Consequently, even the most active compound (**44**) resulting from this work is unlikely to be clinically useful in the treatment of AIDS.

The *gem*-difluorinated alcohols **17**, **18** and **20–24** have shown no interesting activity.

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