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Synthesis of aryl α,α-difluoroethyl thioethers a novel structure motif in organic chemistry, and extending to aryl α,α-difluoro oxyethers

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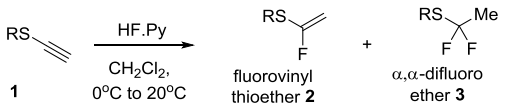
A method for the preparation of aryl α,α-difluoroethyl thioethers ($ArSCF_2CH_3$) is reported and the synthesis approach is extended to aryl α,α-difluoroethyl oxygen ethers. Selected building blocks are further elaborated in cross-coupling reactions and are incorporated into analogues of established trifluoromethyl ether drugs. Conformations are explored and Log P studies of these motifs indicate that they are significantly more polar than their trifluoromethyl ether analogues rendering them attractive for bioactives discovery.

There is considerable interest in novel synthesis methods for the introduction of selectively fluorinated thioethers, and particularly the trifluoromethyl sulfide (R-SCF_3) moiety.[1] The R-SCF_3 group is among the most lipophilic substituents known and it is present in a number of significant pharmaceuticals and agrochemicals products.[2] Also methods have been reported over the years for the preparation of R-SCH_2CF_3 thioethers,[3] and molecules with this substituent have been extensively claimed in the patent literature. Thus selectively fluorinated thioethers have and continue to play an important role as a focus for synthesis methodology and as propriety motifs in bioactives development. We recently noted[4a] the isolation of α,α-difluoroethyl thioethers **3a-c** as hydrofluorination side products of thioacetylene **1a**, in a programme aimed at preparing fluorovinyl thioethers **2a-c**. However increasing the concentration of HF in the pyridine resulted in full conversions to **3a-c** as illustrated in Scheme 1.[4a] A search of the literature indicated that the aryl α,α-difluoroethyl thioether motif **3** had not otherwise been reported in the primary literature and was hardly represented in claimed compounds in patents.



1a R = Bn	50% HF-Py, 4h	100:0	**2a:3a**
	70% HF-Py, 4h	0:100	**2a:3a**
1b R = Ph	50% HF-Py, 10 min	70:30	**2b:3b**
	70% HF-Py, 10 min	0:100	**2b:3b**
1c R = Cyclohexyl	50% HF-Py, 4h	97:3	**2c:3c**
	70% HF-Py, 4h	0:100	**2c:3c**
1d R = 4-Phenylbutyl	50% HF-Py, 4h	91:9	**2d:3d**
	70% HF-Py, 4h	0:100	**2d:3d**

Scheme 1 Hydrofluorination of ethynyl thioethers **1** generate different product ratios with different HF concentrations in pyridine.[4a]

Given its close similarity to the extensively explored R-SCF_3 and R-SCH_2CF_3 substituents, it appeared appropriate to develop a practical preparation of α,α-difluoroethyl thioethers. More generally there are attractive features of a mixed fluorine/hydrocarbon motif which will suppress metabolic oxidation but should be less hydrophobic than the much more common R-SCF_3 ethers[1] as well as R-OCF_3 ethers.[1g,5]
This arises due to the polarized nature of the methyl group hydrogens. The advantages of such partially fluorinated motifs are currently being discussed[6] in the context of pharmacokinetic profiling during small molecule bioactive product development. Despite the contemporary interest in selectively fluorinated thioethers we could not find any other preparations of the α,α-difluoroethyl thioether moiety in the literature, and the structural simplicity of the R-SCF_2Me group makes it an attractive substituent for selection. Therefore in this paper we report exemplification of the reaction in Scheme 1.

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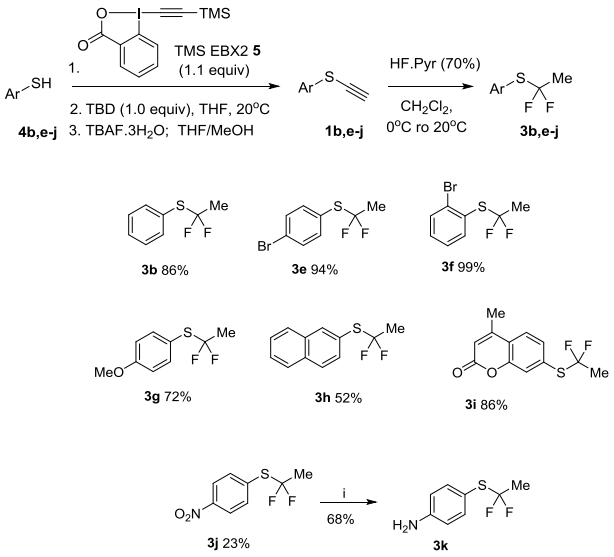
To this end a series of ethynyl aryl thioethers **3b,e-j** were prepared as illustrated in Scheme 2. Our preferred method for the preparation of **3b,e-j** involved the direct acetylenation of



Scheme 2 Ethynyl thioethers **1b,e-j** were prepared by the method of Waser using TMS EBX2 **5**.[7] **1b,e-j** were then treated with HF.Pyr (70%) to generate α,α,α-difluoroethyl thioethers **3b,e-j** products. i. $SnCl_2$, HCl.

thiophenols **4b,e-j** using the iodonium reagent TMS-EBX2 **5**, a modification of the method previously described by Waser.[7] This generated the trimethylsilyl protected ethynyl thioether, where the silyl group was removed prior to work up with tetrabutylammonium fluoride (TBAF). The ethynyl aryl thioethers **1b,e-j** could then be converted to the corresponding α,α-difluoroethyl thioethers **3b,e-j** after treatment with HF.Pyr (70%). This reaction required an excess of HF.Pyr (4 equiv) for efficient conversions. The range of products in Scheme 2 was prepared by this method, and in general the yields were good although the nitroaryl substrate was poorly converted to **3j**.

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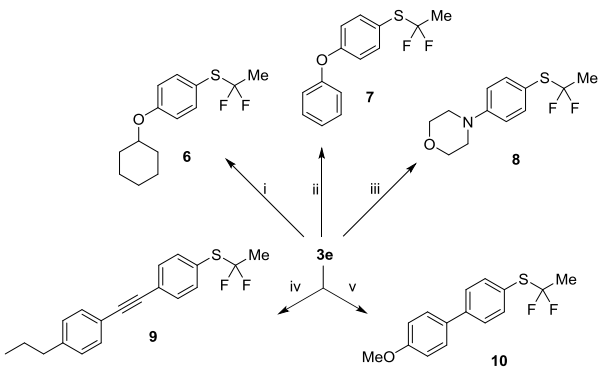
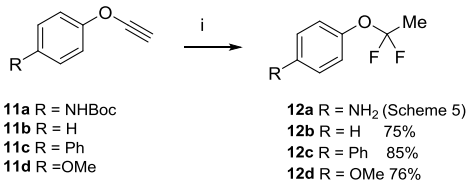


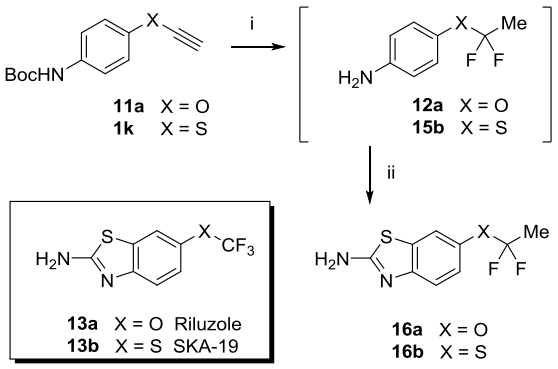
Scheme 3 Cross-coupling reactions of **3e**; i. CuI (cat), K_3PO_4, piconolic acid (cat), cyclohexanol, **3e** in DMSO, 100°C, 24h, 49%; ii. CuI (cat), K_3PO_4, piconolic acid (cat), cyclohexanol, DMSO, **3e**, 100°C, 24h, 43%; iii. $Pd(dba)_3$ (5 mol %), BINAP, 18-crown-6, tBuONa, toluene, 35°C, 18h, 73%; iv. CuI (cat), $PdCl_2(PPh_3)_3$ (cat), NEt_3, DMF, **3b**, 1-ethynyl-4-propylbenzene, 80°C, 6h, 65%; v. H_2O, K_2CO_3 (3 eq), $Pd(PPh_3)_4$, (pOMePh)-boronic acid, **3b**, toluene, 80°C, 16h; 91%.

Despite this, product **3j** was efficiently converted to aniline **3k** after $SnCl_2$/HCl reduction, illustrating the stability of the aryl α,α-difluoroethyl thioether to acidic conditions. Arylbromide **3e** was subject to a range of cuprate and palladium cross coupling reactions as illustrated in Scheme 3 to generate products **6-10**. The chemistry was also applied to prepare oxygen linked α,α-difluoroethyl ethers **12**. Although there is a rich chemistry around the preparation of trifluoromethyl (R-OCF_3) ethers,[8] methods to α,α-difluoroethyl ethers **12** are few. The most widely described method involves variations on the treatment of phenol acetates with XeF_2 to generate α,α-difluoroethyl aryl ethers **12** after a rearrangement[9] and there are earlier accounts which report on the preparation of α,α-difluoro alkylethers from the treatment of thiocarboxylic esters with fluorination reagents.[10] Most recently a reaction of phenols with 1,1-difluorobromoethane, followed by reductive organobromine removal was used to prepare a heteroaryl α,α-difluoroethyl ether.[11] For our purposes the method started with ethynyl ethers **11**.[12] Substrates **11a-d** were treated with HF. Pyr (70%) to deliver the corresponding products **12a-d** as illustrated in Scheme 4.



Scheme 4. New route to α,α-difluoroethers **12a-d**; i. HF.Pyr (70%).

Riluzole **13a**[13] which contains a $ROCF_3$ ether moiety is a drug licensed to treat amyotrophic lateral sclerosis, a form of motor neurone disease, and anxiety. The R-SCF_3 analogue SKA-19 **13b**,[14] has been shown to be a potent anticonvulsant. In order to exemplify the introduction of these α,α-difluoroethyl ether motifs in a drug analogue synthesis both **16a** and **16b** were prepared from the corresponding Boc protected ethynyl ethers **11a** and **1k** respectively as illustrated in Scheme 5. For these synthesis sequences the intermediate anilines **12a** and **15b**.



Scheme 5. Synthesis of analogues **16a** and **16b** of the drugs **13a** and **13b**; i. HF.Pyr (70%), CH_2Cl_2, 0°C, 8h then; ii. Potassium thiocyanate (4 eq), AcOH, then Br_2 in AcOH, 35°C, 24h, 38%.

were not isolated, but were progressed *in situ* to the desired drug analogues **16a** and **16b**.

In general the introduction of aryl-XCF_3 and higher perfluorinated ethers into organic compounds will act to increase lipophilicity, however there is an increasing awareness that partial fluorination introduces orientated molecular dipoles[6] and the inductive effect of fluorine polarises vicinal hydrogens. This can be expected to increase their hydrogen bonding capacity with water, relative to the hydrocarbon. However for the aryl -SCF_2Me and -OCF_2Me ethers the polarisation of the methyl hydrogens will be countered by suppression of lone pair donor ability due to the geminal fluorines, thus it was of interest to explore the influence of partial fluorination in this case. Therefore the Log P's of the aryl-SCF_2Me and aryl-OCF_2Me motifs were measured relative to related motifs which are much more widely used in discovery chemistry. Log P values are compared in Figure 1.

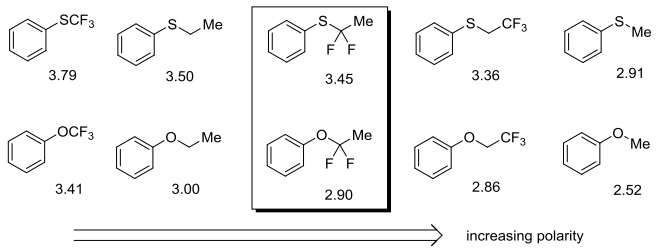


Figure 1 Log P values of aryl derivatives of the α,α-difluoroethyl thioether and oxyether substituents (boxed) with values of related motifs for comparison. Log P values were measured by C_{18} reverse phase HPLC (acetonitrile/water) referenced to standard compounds.

The mixed hydrocarbon/fluorocarbon motifs are significantly more polar than aryl-XCF_3 in both the oxygen and sulfur series, and they have similar, or are slightly more polar, than their corresponding hydrocarbon ethyl ethers (ArXEt), despite the addition of two ($ArXCF_2CH_3$) or three ($ArXCH_2CF_3$) fluorines to the ethyl substituent. This polarity is apparent from calculated electrostatic potential surface maps of the phenyl thio **3b** and oxy **12c** ether analogues. Both have a similar electrostatic profile showing electronegative (red) density around the heteroatom and electropositive density (blue) around the methyl groups as illustrated in Figure 2.

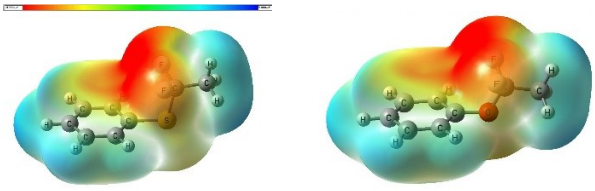


Figure 2: Electrostatic potentials for **3b** (left) and **12c** (right) at the B3LYP/6-311+G(2d,p) level, plotted on a colour scale from -0.003 a.u. (red) to +0.003 a.u. (blue) and mapped onto an isodensity surface ($\rho = 4{\cdot}10^{-4}$ a.u.).

It is well known that $ArOCF_3$ ethers[15] and $ArSCF_3$ thioethers[16] adopt conformations where the Ar-CF_3 bond lies perpendicular to the plane of the aromatic ring. This contrasts with the corresponding ArOMe and ArSMe hydrocarbon ethers which prefer an in plane arrangement. For the $ArXCF_2CH_3$ motifs considered here the replacement of a fluorine for a methyl group (F for Me change) in each case will make the alkyl substituent less electron-withdrawing, but will increase its steric impact, so it became relevant to explore the relative conformer energies. In this context a DFT based analysis was carried out.[17-19] Full geometry optimisations were performed in the gas phase at the B3LYP/6-31+G(d,p) level, followed by computation of the harmonic vibrational frequencies at the same level and single-point energy calculations at the B3LYP-D3/6-311+G(2d,p) level (at that level, the aforementioned conformational preferences of the Me and CF_3 ethers are well reproduced, see Figure SX in the Supporting Information). The relative energies for the difluoroethyl ethers are summarised in Figure 3.

When a fluorine atom in the trifluoromethyl ethers is replaced with a methyl group, the preference for a perpendicular orientation of the resulting difluoroethyl group decreases slightly (20-30%), but it is still predominant particularly for the thio ethers. In-plane conformations are only obtained when the C-Me group is *anti* to the aryl-X bond. The corresponding *gauche* rotamers (which cannot be fixed by imposing symmetry)

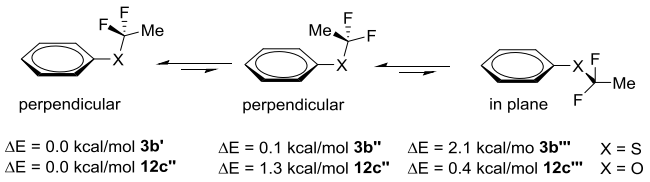


Figure 3 DFT calculations indicate a perpendicular over in-plane conformational preference for $ArXCF_2CH_3$ ethers **3a** and **12c**. Details in SI.

optimise directly to the corresponding perpendicular *gauche* conformers. The perpendicular conformers with an *anti* orientation of the C-Me groups are the most stable, but the *gauche* rotamers are close in energy so that both should be relevant in solution. For instance for the thioether **3b**, the computed difference in ΔG, 0.8 kcal/mol., translates to an equilibrium composition of **3b':3b"** of ca. 64:36 at room temperature.

In conclusion we report a preparation of the α,α-difluoroethyl thioether moiety and present it as a new motif in organic chemistry. The chemistry is extended to a novel approach to the α,α-difluoroethyl oxygen ether series. These motifs are more polar than the OCF_3 and SCF_3 groups, as measured by relative Log P values of their aryl derivatives, and become candidate substituents for medicinal and agrochemical discovery programmes.

Conflicts of interest

There are no conflicts to declare.

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