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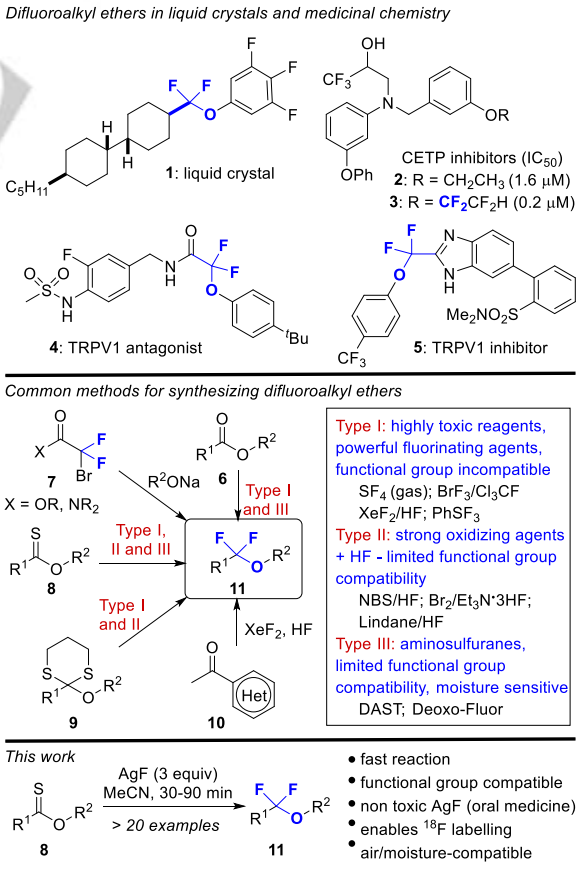
A Convenient Synthesis of Difluoroalkyl Ethers from Thionoesters using Silver(I) Fluoride

Josiah Newton,[a,b] Daniel Driedger,[b] Matthew B. Nodwell,[a] Paul Schaffer,[d] Rainer E. Martin,[c] Robert Britton,[a]* Chadron M. Friesen[b]*

Abstract: Herein we report the mild and rapid fluorodesulfurization of thionoesters using only silver(I) fluoride. This reaction demonstrates excellent functional group tolerance and compliments existing strategies for difluoroalkyl ether synthesis, which rely on toxic and often dangerous reagents that demonstrate limited functional group compatibility. We additionally report the translation of this finding to the production of ^{18}F-labeled difluoroalkyl ethers using fluoride-derived [^{18}F]AgF. This new process should enable the synthesis of a wide range of difluoroalkyl ethers with applications in medicinal and materials chemistry, and radiotracer production.

Difluoroalkyl ethers are found in a variety of compounds ranging from liquid crystals (LCs)[1] to pharmaceuticals[2] and agrochemicals[3] (Figure 1). This highly polarized functional group has been shown to increase dielectric anisotropy and stability while broadening the nematic phase range of LCs, all of which are favorable application-relevant properties.[4] In medicinal chemistry, difluoroalkyl ethers can enhance metabolic stability[2] and impart unique conformational properties[5] to molecules. For example, difluoroalkylaryl ethers have a small barrier to rotation around the ArO-CF_2R bond and can access perpendicular or 'out of plane' conformers that are not readily adopted by the parent alkylaryl ethers.[5b] This conformational flexibility is critical to the 8-fold increase in potency of aryl ether **3** over the parent hydrocarbon **2**.[5a] Likewise, difluoroalkyl ethers have been incorporated in both transient receptor potential vanilloid 1 (TRPV1) antagonists (e.g., **4**)[6] and inhibitors (e.g., **5**)[7] and this functionality is prevalent among the halogenated ether anesthetics typified by methoxyfluorane ($Cl_2CHCF_2OCH_3$).[8] Considering the widespread applications of difluoroalkyl ethers, many strategies have been developed for their synthesis, some of which are summarized in Figure 1. Prominent among these approaches is fluorodesulfurization[9] using highly reactive fluorinating agents including SF_4 gas[9b] or BrF_3[9c] (Type I), or combinations of oxidizing agents with hydrofluoric acid (Type II).[1b,9a,10] Alternatively, both DAST and DeoxoFluor (Type III)[11] have demonstrated utility in the deoxyfluorination or fluorodesulfurization of esters[12] or thionoesters,[12-13] respectively. As a strategic alternative, the rearrangement of heteroaryl ketones using XeF_2 and HF/pyr[5b] or displacement of bromide from α,α-difluoro-α-bromo esters[14] and amides[15] (e.g., **7** → **11**) are also employed for the synthesis of difluoroalkyl ethers (e.g., **4**)[6] and heterobenzylic difluoro ethers (e.g., **5**).[7] Unfortunately, many of the reagents relevant to the synthesis of difluoroalkyl ethers are toxic, dangerous to handle, and react violently with water. Owing to this extreme reactivity, use of these reagents is often limited to substrates devoid of unprotected functional groups and under strictly anhydrous reaction conditions. Here we report the use of Ag(I)F for the conversion of thionoesters into difluoroalkyl ethers, a reaction that does not require anhydrous conditions. This mild, non-toxic reagent represents an excellent alternative to traditional fluorodesulfurization and enables the production of ^{18}F-labelled difluoroalkyl ethers for positron emission tomography (PET) imaging applications.

Figure 1. Difluoroalkyl ethers in materials and pharmaceutical research, and methods for their preparation.



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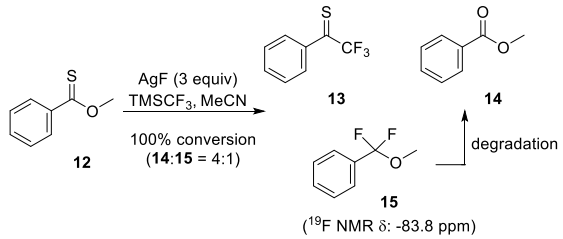

Scheme 1. Discovery of AgF-promoted difluoroalkyl ether synthesis.

Table 1. Optimization of AgF-promoted difluoroalkyl ether synthesis.

entry	solvent	conditions[a] (equiv)	time (h)	conversion (%)[b]
1	C_6H_6	AgF (3)	1	61
2	hexane	AgF (3)	1	56
3	acetone	AgF (3)	1	52
4	**MeCN**	**AgF (3)**	**0.5**	**95**
5	MeCN	AgF (3)	0.2	68
6	MeCN-CH_2Cl_2[c]	AgF (3)	1	89
7	MeCN-acetone[c]	AgF (3)	2	80
8	MeCN	AgF (3) H_2O (2)	0.5	85[d]
9	MeCN	AgF (2) Ag_2O (1)	1.5	79[e]
10	MeCN	$AgBF_4$ (3)	1.5	0
11	MeCN	AgOTf (3) TBAT (3)	2	15[f]
12	MeCN	$AgNO_3$ (3) KF (3), 18-C-6 (0.1)	2	10[g]

[a] Reaction conditions: MeCN (1 mL) was added to vial containing **14** (0.1 mmol) and Ag(I) salt and mixture was stirred at rt; [b] conversion determined by analysis of ^{1}H-NMR spectrum recorded on crude reaction mixture; [c] 1:1 mixture of solvents; [d] butyl benzoate formed in 15%; [e] butyl benzoate formed in 20%; [f] butyl benzoate formed in 49%; [g] butyl benzoate formed in 90%. TBAT = tetrabutylammonium difluorotriphenylsilicate; 18-C-6 = 1,4,7,10,13,16-hexaoxacyclooctadecane.

During studies directed towards the synthesis of trifluoromethyl thioketones (e.g., **13**) we were interested in exploring the fluoride promoted reaction of the Ruppert-Prakash reagent ($TMSCF_3$)[16] with thionoester **12** (Scheme 1). Surprisingly, when AgF was employed as the fluoride source the reaction produced a mixture of ester **14** and the ether **15**, which displayed a resonance characteristic for a difluoroalkyl ether at approximately -84 ppm in the ^{19}F NMR spectrum. While the reaction of AgF with carbon disulfide[17], thiocarbamoyl fluorides[18] and thionocarbonates[18c] has been reported, its use in the direct conversion of thionoesters into difluoroalkyl ethers is without precedent. Considering difluoroalkyl ethers are prone to hydrolysis and liberation of HF "as evidenced by etching of glass vials"[13] it is likely that ester **14** is in fact a degradation product of the difluoroalkyl ether **15**. Based on this observation and the volatility of **15** (bp ~ 110 °C), we further investigated this unusual transformation using thionoester **16**, derived from butyl benzoate. As indicated in Table 1, entries 1-7, a solvent screen revealed that MeCN was the in fact the optimal solvent for this reaction, delivering the difluoroalkyl ether **17** in excellent yield after only 30 min (entry 4). Remarkably, this straightforward process is fully compatible with acetone (entries 3 and 7) and tolerates water (entry 8), in stark contrast to all other reagents employed in the fluorination of thionoesters (Figure 1). Various other combinations of Ag(I) salts and fluoride sources (entries 9-12) highlighted AgF as the optimal reagent for this reaction (see Supporting Information for additional examples), with most other Ag(I) salts promoting hydrolysis of the thionoester or difluoroalkyl ether product.

To rapidly evaluate functional group compatibility, the reaction described in Table 1 entry 4 was repeated in the presence of various additives. Here, we found that functional groups in acetophenone, 1,4-diazabicyclo[2.2.2]octane (DABCO), 4-bromobenzyl bromide, benzaldehyde, benzyl alcohol, 2-phenylethanol, triphenylphosphine, phenyl acetylene, *N*-benzyl benzamide, and styrene oxide (each 1-3 equiv.) had little to no influence on reaction yield (see Supporting Information for details). Conversely, the addition of benzoic acid, heptanal and phenol each reduced product yield to ~30%, while aniline and 2-phenyl ethanethiol practically inhibited fluorination (yield of **17** ~ 10%). The collection of functional groups tolerated by this process clearly differentiate AgF fluorination from all existing fluorination strategies used to prepare difluoroalkyl ethers (Figure 1). Considering that AgF is similar in cost to aminosulfuranes and relatively non-toxic, this convenient process represents an excellent alternative to all existing strategies used for the fluorination of thionoesters. To assess the scope of AgF fluorination, several thionoesters were readily prepared through reaction of the corresponding ester with Lawesson's reagent,[19] and/or transesterification.[10] As summarized in Figure 2, a wide range of thionoesters could be rapidly converted into difluoroalkyl ethers at room temperature using this straightforward protocol. Notably, acid-sensitive functionalities including oxetanes and acetals were fully compatible as were several heterocycles (e.g., furan, pyrrolidine, thiazole, pyridine, indole and indazole) and a quaternary ammonium function (**26**). Moreover, primary alcohol functions that are readily fluorinated by aminosulfuranes were predictably unaffected by AgF, though they can intercept the oxocarbenium ion intermediate formed during this reaction (*vide infra*). The aryl ethers **27**, **35** and **37** could also be readily prepared from the corresponding thionoesters, though here a reaction temperature of 80 °C was required. The selectivity for thionoesters over other carbonyls is also highlighted in the fluorination of a glyoxylate derivative, which provided the difluoroketone **36** in good yield. It is notable that while the majority of products could be isolated and purified by silica gel chromatography or simple filtration through Celite® 545, in several instances the difluoroalkyl ether products were partially hydrolyzed to the corresponding ester (e.g., **39** - **43**) or degraded completely (see Supporting Information) during isolation and/or purification. In general, we found that electron rich aryl and heteroaryldifluoroalkyl ethers were the most prone to degradation. The instability of these compounds is similar to that of 5-

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membered heteroaromatic difluoromethylenes, which readily hydrolyze to the corresponding aldehyde. [20]

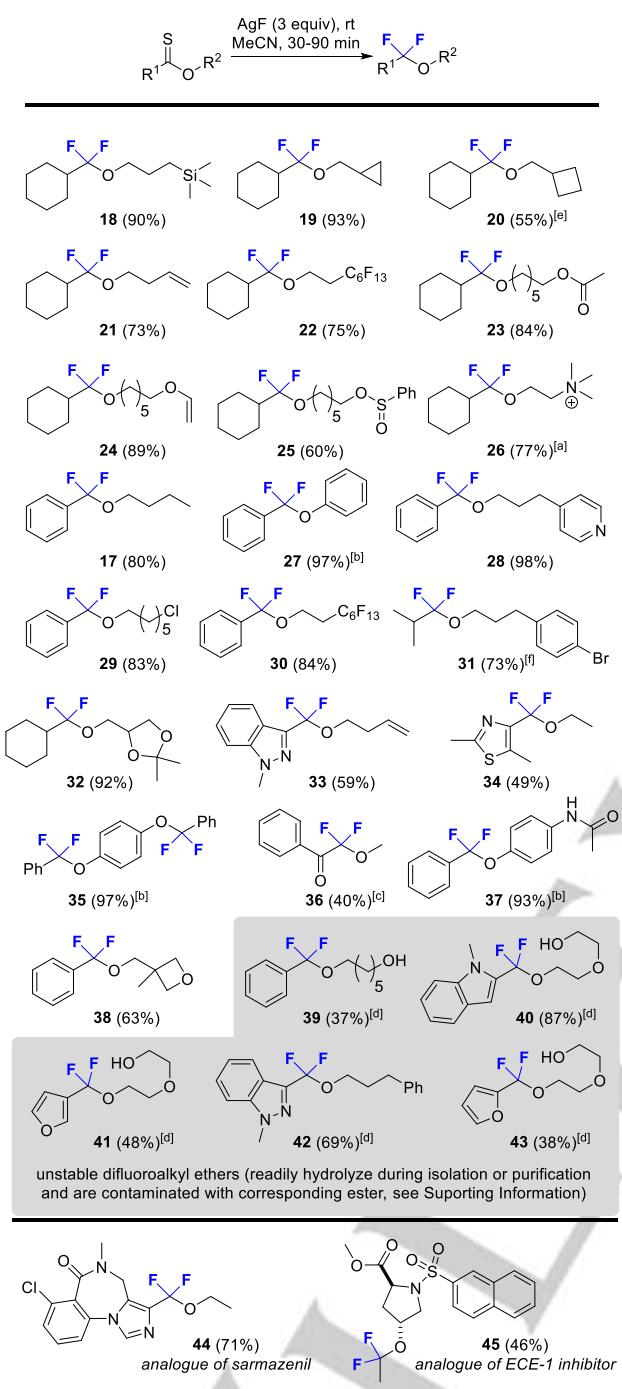
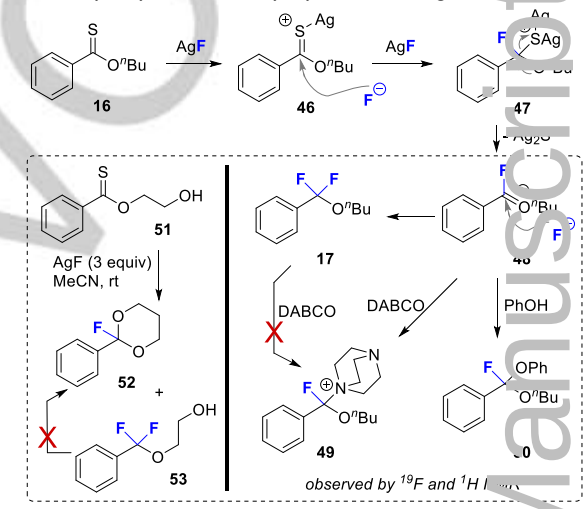


Figure 2. Scope of difluorination of thionoesters with AgF. Reaction conditions: a solution of the thionoester (0.1 mmol) and AgF (0.3 mmol) in MeCN (1 mL) was stirred at rt for 30-90 min (isolated yields reported unless indicated otherwise); [a] product is inseparable from the corresponding ester, which was produced in 23% yield; [b] reaction at 90 °C for 90 min; [c] product is inseparable from the corresponding ester, which was produced in 50% yield; [d] yield calculated from analysis of ^{1}H NMR spectra for unstable difluoroalkyl ethers. [e] product is inseparable from the corresponding ester, which was produced in 23% yield. [f=] product is inseparable from the corresponding ester, which was produced in 27% yield

From a mechanistic perspective, we propose that AgF fluorination of thionoesters involves coordination of Ag(I) to the thiocarbonyl, which is then activated for nucleophilic attack by fluoride (e.g., **46** → **47**). A subsequent reaction with a second equivalent of Ag(I) produces Ag_2S and an oxocarbenium ion **48** that is then trapped by fluoride. This proposal is supported by experiments that demonstrate both intra- and intermolecular trapping of the oxocarbenium ion intermediate. Specifically, we found that reaction of thionoester **51** provided the cyclic fluoroacetal **52** in addition to the expected difluoroalkyl ether **53**. Notably, the difluoroalkyl ether **53** slowly degraded to (2-hydroxyethyl) benzoate (not shown) and not the fluoroacetal **52**. Additionally, during functional group compatibility studies involving **16**, we observed the DABCO and phenol adducts **49** and **50**, respectively. Treating the purified difluoroalkyl ether **17** with DABCO in MeCN for 2 h provided none of the DABCO adduct **49** indicating that the later compound is not product derived.



Scheme 2. Mechanistic insight from oxocarbenium ion trapping experiments.

We then examined the feasibility of applying this reaction to the radiosynthesis of ^{18}F-labelled difluoroalkyl ethers. Previously, Gouverneur had demonstrated the ^{18}F-labeling of α,α-difluoro-α-(aryloxy)acetic acid derivatives via halogen exchange on the corresponding α-bromo-α-fluoro precursor.[21] An ^{18}F for ^{19}F isotopic exchange reaction has also been reported for the preparation of 1,1-difluoro-2,2-dichloroethyl aryl ethers.[22] The mild conditions of the AgF/thionoester transformation - rapid fluorination at room temperature, water tolerance, and independence from phase transfer catalysts avoid many of the harsh conditions typically encountered in ^{18}F radiosynthesis. As such, this transformation could prove useful for the radiolabeling of sensitive molecular scaffolds.

Here, we followed the protocol recently reported by Sanford and Scott [23] for the preparation of [^{18}F]AgF. Elution of trapped [^{18}F]fluoride from a quaternary ammonium cartridge using AgOTf

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provided an aqueous solution of [^{18}F]AgF. The [^{18}F]AgF was then azeoptropically dried, and MeCN was added followed by the thionoester. The reaction mixture was then heated to 80 °C for 20 min, filtered and examined by HPLC. These operationally simple reactions were exceptionally clean and exhibited good to excellent radiochemical conversion (RCC) to the corresponding ^{18}F-difluoroalkyl ethers [^{18}F]**27**, [^{18}F]**31** and [^{18}F]**44** (Figure 3). For these proof-of-concept studies, AgF carrier was added. Thus, in its present form this radiosynthesis of ^{18}F-difluoroalkyl ethers may not be suitable for some imaging applications. However, decreasing the amount of [^{19}F]AgF or omitting [^{19}F]AgF altogether should enable production of radiotracers with clinically relevant specific activities and will be the subject of further examination.

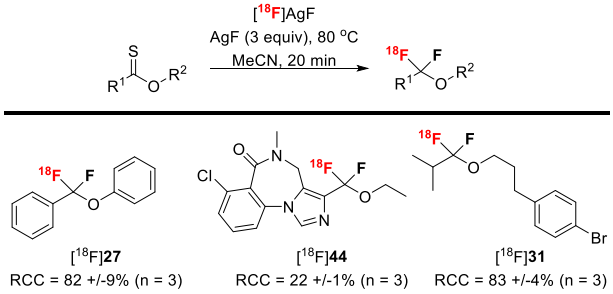

Figure 3. Synthesis of ^{18}F-labelled difluoroethers using [^{18}F]AgF. General conditions: a solution containing [^{18}F]AgF (70-250 MBq), [^{19}F]AgF (3 equiv), and thionoester in MeCN (0.6 mL) was heated to 80 °C for 20 min. RCC was calculated by % integrated area of the ^{18}F product versus [^{18}F]fluoride in a radio-HPLC trace.

In summary, we have developed a new method for the synthesis of difluoroalkyl ethers that involves the direct fluorodesulfurization of thionoesters with Ag(I)F at room temperature. This mild and rapid reaction tolerates a wide range of functional groups and water, clearly differentiating it from the many existing syntheses of difluoroalkyl ethers that generally rely on toxic and/or dangerous reagents. These qualities also make this process useful for the production of radiotracers using [^{18}F]AgF, which we demonstrated in three examples including the preparation of an ^{18}F-labelled analogue of sarmazenil, a partial inverse agonist of benzodiazepine receptors. The ready access to difluoroalkyl ethers enabled by this convenient strategy should enable the further study of this functional group for materials and medicinal chemistry, and inspire new applications in radiochemistry.

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Keywords: difluoroether • fluorodesulfurization • silver(I)fluoride • ^{18}F-labelling • radiotracer

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