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Lewis acid-promoted hydrofluorination of alkynyl sulfides to generate α-fluorovinyl thioethers

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Full Research Paper

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Abstract

A new method for the preparation of α-fluorovinyl thioethers is reported which involves the hydrofluorination of alkynyl sulfides with $3HF{\cdot}Et_3N$, a process that requires Lewis acid activation using $BF_3{\cdot}Et_2O$ and TiF_4. The method gives access to a range of α-fluorovinyl thioethers, some in high stereoselectivity with the *Z*-isomer predominating over the *E*-isomer. The α-fluorovinyl thioether motif has prospects as a steric and electronic mimetic of thioester enols and enolates, important intermediates in enzymatic C–C bond forming reactions. The method opens access to appropriate analogues for investigations in this direction.

Introduction

Organofluorine compounds have found wide use in tuning the properties of performance compounds in medicinal and materials chemistry [1,2]. Also the electronegativity of fluorine has been used to design and tune steric and electronic mimetics of functional groups for applications in biomolecular chemistry. For example as illustrated in Figure 1, CF_2-phosphonates became popular mimetics of the phosphate group [3,4], and vinyl fluorides were developed as analogues of the amide bond [5]. Difluorotoluene has proved to be a good spacial mimetic of the thymine base in thymidine, and has been shown to act as a functional and complementary template in enzymatic DNA synthesis [6].

We have recently begun to explore synthesis methods to prepare α-fluorovinyl thioethers, to open up the possibility of exploring this motif as a mimetic for enols and enolates of biochemically relevant thioesters. Thioesters of low molecular weight carboxylic acids are found widely in metabolism, often as their co-enzyme A esters, and they then undergo condensation reactions through enols or enolates to generate C–C bonds typified by the processes of long chain fatty acid biosynthesis. α-Fluorovinyl thioethers, illustrated in Figure 2, have a spatial and electrostatic profile consistent with the potential to mimic these enzyme intermediates.

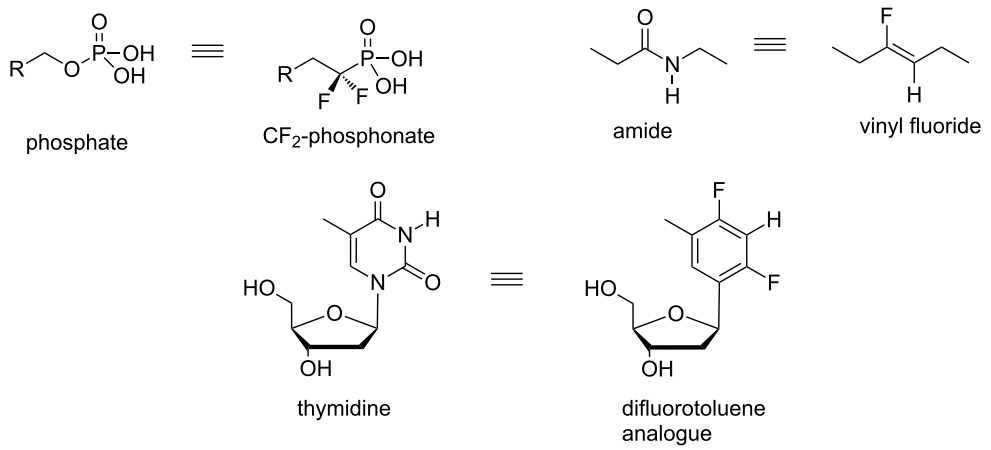


Figure 1: Some spacial and electronic mimetics with fluorine as a design feature [3-6].

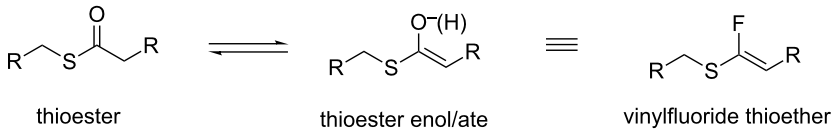


Figure 2: α-Fluorovinyl thioesters offer prospects as thioester enol/ate mimetics [7].

There is limited literature for preparing such analogues. We have previously described the preparation of α-fluorovinyl thioethers by hydrofluorination of the corresponding alkynyl sulfides using HF·Py [7]; in this article we wish to report an improved synthesis of α-fluoroalkenyl thioethers via Lewis acid-mediated hydrofluorination of alkynyl sulfides, a method which brings us closer to being able to prepare analogues of particular design for enzyme inhibition studies.

Results and Discussion

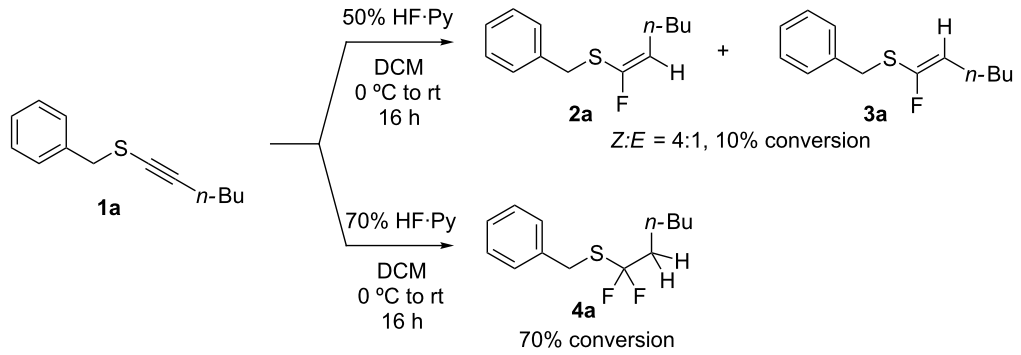
Several methods for the synthesis of vinyl thioethers have been reported, including Wittig reactions [8], ionic and radical additions of thiols to alkynes [9] and coupling of 1-alkenyl halides with thiols, among others [10,11]. However, the literature for the preparation of α-fluorovinyl thioethers is somewhat scarce. The only account we are aware of involves the AIBN-promoted thiodesulfonylation of aromatic fluorovinyl sulfones as reported by Wnuk [12], a reaction which works in varying yields and stereoselectivities.

Following from our previous experience [7] with terminal acetylene thioethers, we now explore this reaction with alkynyl sulfides. In this regard **1a** [13] was used as a model substrate and was treated with 50% HF·Py in dichloromethane. This, however, resulted in a very poor conversion (~10%) and gave a 4:1 product mixture of the fluorinated products **2a** and **3a** as illustrated in Scheme 1. When 70% HF·Py was employed, up to 70% conversion was achieved, but with over-fluorination to generate only the difluoromethylene thioether **4a** (not isolated).

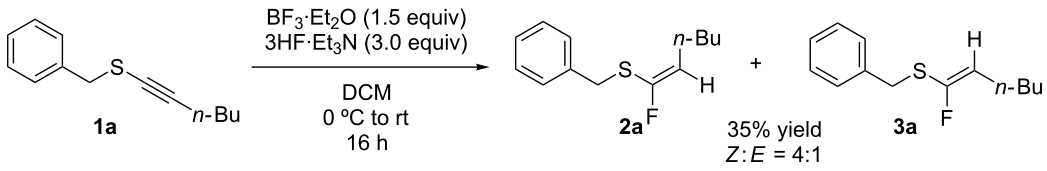
In view of the lack of control with HF·Py attention turned to triethylamine trihydrogen fluoride ($3HF{\cdot}Et_3N$). This proved unsuccessful presumably as it is a less acidic reagent compared to HF·Py, and thus activation of alkynyl sulfide **1a** was explored by addition of a Lewis acid.

At this stage we were pleased to find that the use of $BF_3{\cdot}Et_2O$ allowed for a conversion of over 90% of **1a** (16 h at room temperature). However, products **2a** and **3a** were obtained as a 4:1 mixture of *Z*/*E*-isomers, and they could only be isolated in a modest yield (35%) as shown in Scheme 2 and Table 1 (entry 7).

Encouraged by this result, a number of Lewis acids were tested, including $SnCl_2$, $ZnCl_2$, $Sc(OTf)_3$, $AuCl{\cdot}SMe_2$ and $B(C_6F_5)_3$ (Table 1). The Lewis acids (1.5 equivalents) were added to a mixture of sulfide **1a** and $3HF{\cdot}Et_3N$ (3.0 equivalents) at 0 ºC, but no reactions took place under these conditions. The $HBF_4{\cdot}SiO_2$ reagent was chosen as a solid phase-supported HBF_4 equivalent [14]; carrying out the reaction in the presence of this reactant and $3HF{\cdot}Et_3N$ led to complete decomposition of sulfide **1a**.



Scheme 1: HF·Py mediated hydrofluorinations of **1a**.



Scheme 2: $BF_3{\cdot}Et_2O$/3HF·Et_3N mediated hydrofluorination of **1a**.

Table 1: Lewis acid screening.

Entry	Lewis acid	HF source	Time	Temp	Conversion	Yield	*Z/E*
1	$SnCl_2$	3HF·Et_3N	16 h	0 °C to rt	0%	–	–
2	$ZnCl_2$	3HF·Et_3N	16 h	0 °C to rt	0%	–	–
3	$Sc(OTf)_3$	3HF·Et_3N	16 h	0 °C to rt	0%	–	–
4	$SiO_2{\cdot}HBF_4$	3HF·Et_3N	16 h	0 °C to rt	n.a.[a]	–	–
5	$AuCl{\cdot}SMe_2$	3HF·Et_3N	16 h	0 °C to rt	0%	–	–
6	$B(C_6F_5)_3$	3HF·Et_3N	16 h	0 °C to rt	0%	–	–
7	$BF_3{\cdot}Et_2O$	3HF·Et_3N	16 h	0 °C to rt	>90%	35%	4:1
8	TiF_4	3HF·Et_3N	16 h	0 °C to rt	70%	42%	4:1

[a]Substrate decomposed.

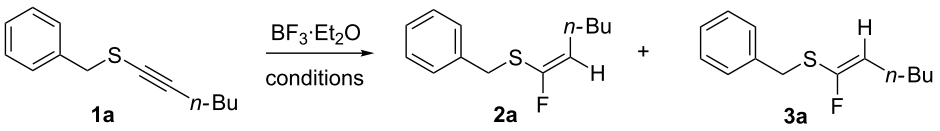
With TiF_4 the overall conversion was around 70%, and the hydrofluorinated product could be isolated in an improved yield (42%, 4:1 *Z:E*).

In order to improve the reaction yields, reactions with the $BF_3{\cdot}Et_2O$/3HF·Et_3N and TiF_4/3HF·Et_3N systems were optimised and the outcomes described in Table 2 and Table 3, respectively. Shorter reaction times (5 h) led to reduced conversions (Table 2, entry 2) and $BF_3{\cdot}Et_2O$ or TiF_4 are required to be stoichiometric, otherwise the reaction does not occur (Table 2, entry 4) and an excess of $BF_3{\cdot}Et_2O$ over the alkynyl sulfide is required for an improved outcome (Table 2, entry 1).

The high conversion of **1a** but low product (**2a** and **3a**) isolation is attributed to substrate decomposition. When the reaction is followed by ^{19}F NMR (vide infra), the presence of the hydrofluorinated products **2a** and **3a** is obvious and the anion BF_4^-, when using $BF_3{\cdot}Et_2O$, or TiF_6^{2-} when using TiF_4 are clearly identifiable. No other fluorinated species are detected, thus it does not appear that products **2a** and **3a** decompose.

A number of attempts were made to improve the yields and reduce starting material decomposition. At low temperatures the reaction is sluggish and conversions are low (~20%), even with prolonged reaction times (5 days, Table 2, entry 5). A second

Table 2: Optimisation of $BF_3{\cdot}Et_2O$/3HF·Et_3N mediated hydrofluorination.



Entry	$BF_3{\cdot}Et_2O$ (equiv)	3HF·Et_3N (equiv)	Time	Temp.	Solvent	Conversion	Yield
1	1.5	3.0	16 h	0 °C to rt	DCM	>90%	35%
2	1.5	3.0	5 h	0 °C to rt	DCM	39%	28%
3	1.0	2.0	16 h	0 °C to rt	DCM	>80%	30%
4	0.5	3.0	16 h	0 °C to rt	DCM	–	–
5	1.5	3.0	5 days	0 °C	DCM	20%	–
6	1.5 × 2	3.0	7 h	0 °C	DCM	20%	–
7	1.5	3.0	5 h	40 °C	DCM	>95%	30%
8[a]	1.5	3.0	16 h	0 °C to rt	DCM	70%	28%
9	1.5 × 2	3.0 × 2	21 h	[b]	THF	25%	–
10	1.5	3.0	16 h	0 °C to rt	DCE	<5%	–
11	1.5	3.0	21 h	[c]	DCE	10%	–
12	1.5 x 2	3.0 x 2	21 h	[d]	DCE	n.a.[e]	–

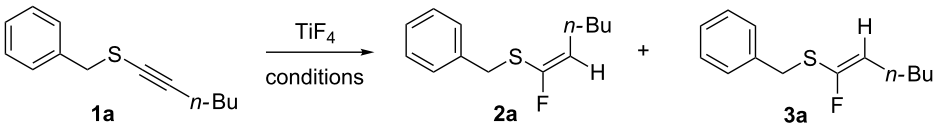
[a]$BF_3{\cdot}Et_2O$ and 3HF·Et_3N were pre-mixed at 0 °C prior to adding starting material **1a**. [b]Mixture stirred for 16 hours at room temperature, then heated to 50 °C for 5 hours. [c]Mixture stirred for 16 hours at room temperature, then stirred under reflux for 5 hours. [d]Mixture stirred for 5 hours at room temperature, then stirred under reflux for 16 hours. [e]Substrate decomposed.

addition of 1.5 equivalents of $BF_3{\cdot}Et_2O$ after a few hours at 0 °C proved ineffective (Table 2, entry 6). On the other hand, warming the mixture to reflux (40 ºC for dichloromethane) allowed for complete conversion in just 5 hours (Table 2, entry 7) although the isolated yield (30%) was relatively modest. Thus heating promotes the reaction but also substrate decomposition. Pre-equilibration of $BF_3{\cdot}Et_2O$ and 3HF·Et_3N at 0 °C prior to starting material **1a** addition resulted in a 70% conversion and a modest 28% yield (Table 2, entry 8). When tetrahydrofuran or dichloroethane were explored as solvents the conversions were low, even when warming (tetrahydrofuran, Table 2, entry 9, dichloroethane, Table 2, entries 10–12).

For the TiF_4/3HF·Et_3N reactions (Table 3) shorter reaction times also afforded lower conversions, and sub-stoichiometric levels of TiF_4 failed to initiate the reaction. Tetrahydrofuran and dichloroethane at different temperatures were again not useful solvents.

Having optimised the reaction to some extent with substrate **1a**, a range of alkynyl sulfides [15] were now prepared and each

Table 3: Optimisation of TiF_4/3HF·Et_3N mediated hydrofluorination.

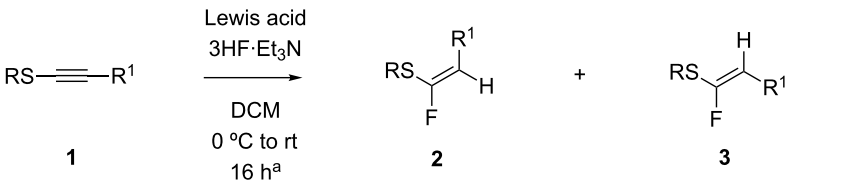


Entry	TiF_4 (equiv)	3HF·TEA (equiv)	Time	Temp.	Solvent	Conversion	Yield
1	1.5	3.0	5 h	0 °C to rt	DCM	39%	–
2	1.5	3.0	16 h	0 °C to rt	DCM	>90%	42%
3	0.5	3.0	16 h	0 °C to rt	DCM	–	–
4	1.5	3.0	16 h	0 °C to rt or reflux	THF	–	–
5	1.5	3.0	16 h	0 °C to rt, then reflux	DCE	10%	–

individually treated with both hydrofluorination protocols using $BF_3{\cdot}Et_2O/3HF{\cdot}Et_3N$ and $TiF_4/3HF{\cdot}Et_3N$. The results are summarised in Table 4. Cyclohexylethynyl(benzyl)sulfane (**1b**) gave an improved outcome relative to **1a** with higher yields and better stereoselectivity. The $BF_3{\cdot}Et_2O$ reaction furnished an inseparable 9:1 mixture of *Z*-**2b** and *E*-**3b** isomers in 48% yield. When TiF_4 was used, the reaction showed complete stereoselectivity, affording the *Z*-isomer of **2b** in 55% yield.

Replacement of the cyclohexyl moiety with a phenyl ring in **1c** led to a fully stereoselective reaction both with $BF_3{\cdot}Et_2O$ and TiF_4, giving the *Z*-stereoisomer **2c** in 45% and 57% yields, res-

Table 4: Scope of $BF_3{\cdot}Et_2O$ and TiF_4-mediated hydrofluorination reaction.



1 **2** **3**

$^{cis}J_{H\text{-}F}$ = 12.7–18.3 Hz $^{trans}J_{H\text{-}F}$ = 29.1–31.9 Hz

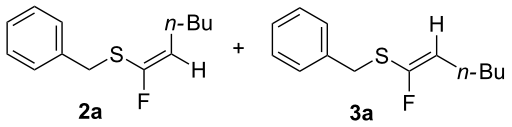
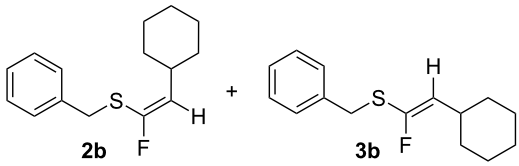
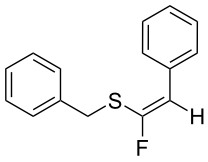
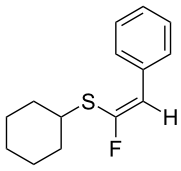
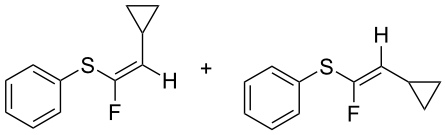
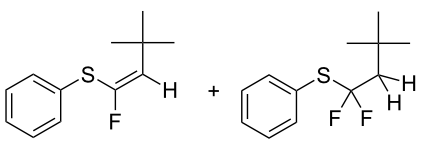
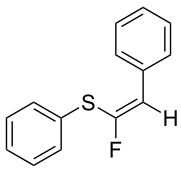
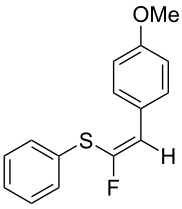
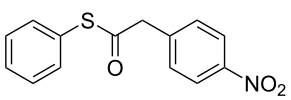
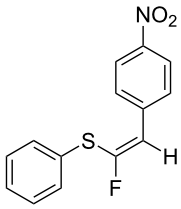
Substrate		Conversion and yield	Products[a]
1a R = Bn R^1 = *n*-Bu	$BF_3{\cdot}Et_2O$	>90%, 35% *Z*/*E* 4:1	 **2a** **3a**
	TiF_4	70%, 42% *Z*/*E* 4:1	
1b R = Bn R^1 = Cy	$BF_3{\cdot}Et_2O$	>90%, 48% *Z*/*E* 9:1	 **2b** **3b**
	TiF_4	80%, 55% *Z* only (**2b**)	
1c R = Bn R^1 = Ph	$BF_3{\cdot}Et_2O$	60%, 45% *Z* only	 **2c**
	TiF_4	>90%, 57% *Z* only	
1d R = Cy R^1 = Ph	$BF_3{\cdot}Et_2O$	complete, 47% *Z* only	 **2d**
	TiF_4	>90%, 68% *Z* only	
1e R = Ph R^1 = cyclopropyl	$BF_3{\cdot}Et_2O$	>80%, 47% *Z*/*E* 3:2	 **2e** **3e**
	TiF_4	90%, 69% *Z*/*E* 7:3	
1f R = Ph R^1 = *t*-Bu	$BF_3{\cdot}Et_2O$	80%, 40% *Z* only (contains 2% **4f**)	 **2f** **4f**
	TiF_4	>90%, 62% *Z* only (contains 2% **4f**)	

Table 4: Scope of $BF_3{\cdot}Et_2O$ and TiF_4-mediated hydrofluorination reaction. (continued)

1g R = Ph R^1 = Ph	$BF_3{\cdot}Et_2O$	75%, 32% *Z* only	 **2g**
	TiF_4	80%, 41% *Z* only	
1h R = Ph R^1 = 4-MeOPh	$BF_3{\cdot}Et_2O$	27%,[b] 9% *Z* only	 **2h**
	TiF_4	35%,[b] 17% *Z* only	
1i R = Ph R^1 = 4-NO_2Ph	$BF_3{\cdot}Et_2O$	90% compound **5** [16], 45% only traces of fluorinated products	 **5**
	TiF_4	15%,[b] 5% *Z* only	 **2i**
1j R = Ph R^1 = 4-CF_3Ph	$BF_3{\cdot}Et_2O$	<5%,[b] NO products isolated	–
	TiF_4	<5%,[b] NO products isolated	

[a]The regiochemistry of all products was determined by NMR analysis. The *Z*/*E* stereochemistry was determined by calculating the vinyl moieties H–F coupling constants. [b]Reaction times were 16 hours for all entries except for substrates **1h**, **1i**, and **1j** (7 days).

pectively. We then maintained the phenyl moiety on the alkyne side of the sulfide, and replaced the benzyl group with a cyclohexyl fragment directly connected to the sulfur atom (compound **1d**). This material allowed too for a stereoselective reaction, giving rise to the *Z*-stereoisomer of **2d** in 47% and 68% yields, respectively. At this stage we decided to explore two simple variations of the groups directly connected to the ethynyl moiety, that are, a cyclopropyl group and the bulky *tert*-butyl group. Thus, we reacted cyclopropylethynyl(phenyl)sulfane (**1e**) with $BF_3{\cdot}Et_2O$, obtaining an inseparable 3:2 mixture of *Z*-**2e** and *E*-**3e** isomers in 47% yield. The reaction with TiF_4 showed a better stereoselectivity, furnishing a 7:3 *Z*/*E* mixture in 69% yield.

Interestingly, the reaction of *tert*-butylethynyl(phenyl)sulfane (**1f**) with $BF_3{\cdot}Et_2O$ and TiF_4, while being completely stereoselective, furnished the *Z*-stereoisomer **2f** in 40% and 62% yields, respectively, along with a 2% of difluorinated compound **4f**. The formation of this byproduct could not be avoided; in fact lower temperatures or shorter reaction times did not change the outcome, and the contaminant **4f** could always be detected (and not removed) from the desired product **2f**.

We were also interested in exploring the electronic effects of *para*-substitution of the phenyl group directly attached to the ethynyl moiety on the reaction outcome; thus we selected compounds **1g–j** and reacted them under our hydrofluorinating conditions. Phenylethynyl(phenyl)sulfane (**1g**) represented the "unactivated" compound in the series. Although the stereoselectivity was complete with the *Z*-isomer of **2g** as the sole product, the yields were unexpectedly low both with $BF_3{\cdot}Et_2O$ and TiF_4 (32% and 41%, respectively).

We thought that the electron-donating 4-methoxy group would release enough electron density towards the triple bond to increase the yields, and possibly shorten the reaction times.

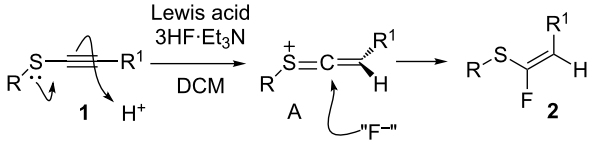
Thus, we prepared compound **1h** and then reacted it with our hydrofluorinating systems; surprisingly, almost no reaction took place during 16 hours, and it was necessary to extend the reaction time to 7 days to obtain the desired product **2h**, which was isolated in 9% yield from the $BF_3{\cdot}Et_2O$ reaction and in 17% when TiF_4 was employed. It appears that the methoxy group is able to efficiently coordinate the Lewis acid reactants and thus almost prevent the reaction from occurring.

Conversely, and as expected, the 4-nitro group had a detrimental effect on the reaction outcome. When 4-nitrophenyl(ethynyl)sulfane (**1i**) was treated with TiF_4, it took nearly 7 days to observe some reaction progress, and the desired *Z*-isomer of **2i** could be isolated in only 5% yield. However, when **1i** was reacted with the $BF_3{\cdot}Et_2O$, the starting material was completely consumed in 16 hours, but only traces of the desired compound **2i** could be detected, with thioester **5** being the main reaction product (45% yield). An explanation for this behaviour can be drawn from the fact that the 4-nitrophenyl group surely must increase the triple bond electrophilicity, hence any trace of water present in the reaction mixture could lead to an intermediate enol thioester which would in turn readily convert to the stable thioester **5**. Nonetheless, ensuring rigorously anhydrous reaction conditions and using fresh $BF_3{\cdot}Et_2O$ could not prevent the formation of **5**, while the same compound was never detected when TiF_4 was used, even after extended reaction times.

Because of the peculiar reactivity of electron-poor alkynyl sulfide **1i** with respect to $BF_3{\cdot}Et_2O$ and TiF_4, we decided to carry out a further test with compound **1j**, with the intention of having the 4-trifluoromethylphenyl group removing electron-density from the triple bond, thus possessing a reactivity similar to that of nitro compound **1i**. Surprisingly, compound **1j** was found mostly unreacted after 7 days, and NMR analysis of the crude reaction mixtures did indicate the presence of product **2j** only in traces (<5% conversion). Since **1j** behaved in a similar way both with $BF_3{\cdot}Et_2O$ and TiF_4, we could only conclude that the formation of thioester **5** from sulfide **1i** was due to some very specific side-reaction promoted by the nitro group, possibly with its participation in the reaction process.

^{19}F NMR was used to probe changes in the Lewis acids in the reaction. Ratios of 1:2 Lewis acid:$3HF{\cdot}Et_3N$ mixtures in CD_2Cl_2 were stirred at room temperature for 2 hours, and the aliquots (0.7 mL) were assayed in Teflon NMR tubes. ^{19}F NMR indicated that for each Lewis acid, BF_3 and TiF_4, respectively had disappeared, forming the corresponding anions BF_4^- (−150.75 ppm) and $[TiF_6]^{2-}$ (75.37 ppm), respectively. Broad peaks corresponding to the excess $3HF{\cdot}Et_3N$ reagent were present. BF_4^- is known to be an inherently inert, non-nucleophilic counter ion; in the case of TiF_4, $[TiF_6]^{2-}$ was the only species present in solution, and we were unable to detect any penta-coordinated $[TiF_5]^-$ species. It has been reported that an excess of hydrofluoric acid positions the equilibrium between $[TiF_5]^-$ and $[TiF_6]^{2-}$ in favour of the latter [17]. Moreover $[TiF_6]^{2-}$ is rather unreactive [18], similar to the BF_4^- anion. We then analysed both reaction mixtures by ^{19}F NMR, separately in CD_2Cl_2, in the presence of sulfide **1a**, after stirring at room temperature for 2 hours. This showed the presence of **2a** and **3a**, as well anions BF_4^- or $[TiF_6]^{2-}$ and also an excess $3HF{\cdot}Et_3N$.

In light of these observations, our working hypothesis is that the Lewis acid acts to increase the acidity of the $3HF{\cdot}Et_3N$ by sequestering fluoride ions as relatively unreactive metal fluorides; thus, the alkynyl sulfides are activated by protonation possibly through an intermediate such as **A** as illustrated in Scheme 3. Such an intermediate would then be susceptible to fluoride ion attack, and progress to the reaction products. The major *cis* stereoselectivity is consistent with the attack of an intermediate such as **A** from the less hindered face, opposite to the R^1 substituent (Scheme 3).



Scheme 3: Proposed Lewis acid-mediated hydroflurination of sulfides **1**.

Conclusion

In summary, we have developed a mild method for the synthesis of α-fluorovinyl thioethers. The method involves the hydrofluorination of alkynyl sulfides by $3HF{\cdot}Et_3N$ and requires activation using $BF_3{\cdot}Et_2O$ or TiF_4. The reactions display moderate to good stereoselectivity in favour of the *Z*-hydrofluorination product, and this opens the way forward for making appropriate analogues as potential steric and electronic mimetics of thioester enols and enolates relevant to particular enzymatic transformations.

Supporting Information

Supporting Information File 1

Experimental part and NMR spectra of synthesised compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-11-205-S1.pdf]

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