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Synthesis of 2-Aryl-3-fluoro-5-silylthiophenes via a Cascade Reactive Sequence

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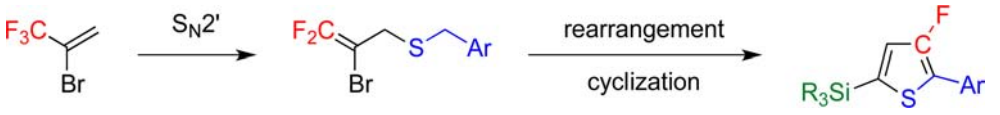
ABSTRACT



2-Aryl-3-fluoro-5-silylthiophenes were readily prepared only in two steps from 2-bromo-3,3,3-trifluoropropene in good yields. These transformations include the first successful S_N2'-type reaction of 2-bromo-3,3,3-trifluoropropene and benzylthiols and [2,3]sigmatropic rearrangement of 2-bromo-3,3-difluoroallyl benzyl sulfide.

The thiophene nucleus is a component of several classes of bioactive natural compounds and functional materials.[1] A facile preparation for multisubstituted thiophenes still remains a challenging task in modern organic chemistry. On the other hand, only a few procedures have been reported for the preparation of fluorothiophenes despite the fact that fluoro substituents are powerful modifiers of chemical and biological properties of organic compounds as reported in many pharmaceuticals and agrochemicals.[2] From a synthetic viewpoint, most methods for the synthesis of fluorothiophenes are based on an application of the substitution reactions of fluorine on the thiophene ring.[3] In contrast to these traditional methods, cyclization approaches to the regioselective synthesis are scarce. To the best of our knowledge, only three groups have reported this methodology for the synthesis of substituted fluorothiophenes.[4]

Our group has been interested in the building block strategy for the introduction of fluorine(s) into organic molecules.[5] To explore the utilization of 2-bromo-3,3,3-trifluoropropene (**1**) as a starting material, we focused on its S_N2'-type reaction. Although similar S_N2'-type reactions have already been reported by several groups,[6] there is only one example of using 2-bromo-3,3,3-trifluoropropene.[7] Herein, for the first time, we report efficient S_N2'-type reactions of **1** with various thiolates, providing highly selective 2-bromo-3,3-difluoroallyl sulfides (**2**). In this study we will report the stepwise synthesis of 2-aryl-3-fluoro-5-silylthiophenes (**10**) in high yield.

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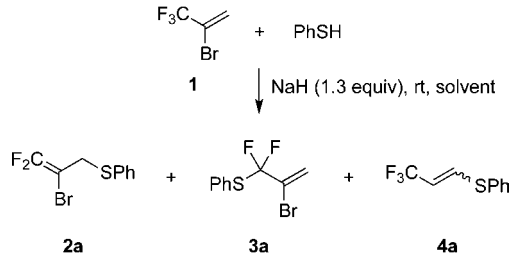
Table 1. Reaction of **1** and Thiophenol under Various Conditions



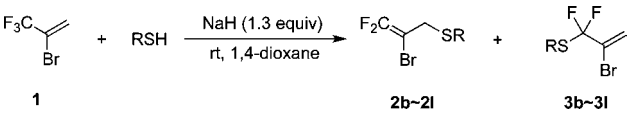
entry	equiv **1**	solvent	time [min]	yield[a] [%]	**2a:3a:4a**[b]
1	3.0	THF	60	57	80/20/0
2	3.0	1,4-dioxane	360	73	93/7/0
3	1.0	1,4-dioxane	360	66	87/13/0
4	5.0	1,4-dioxane	360	69	96/4/0
5	3.0	DMF	10	trace[c]	–
6	3.0	DMSO	10	trace[c]	–
7	3.0	MeCN	10	trace[c]	–
8	3.0	ether	240	NR[d]	–
9	3.0	toluene	240	NR[d]	–
10[e]	1.2	EtOH	480	94	0/0/100

[a] Isolated combined yield. [b] The ratio was determined by ^{19}F NMR spectroscopy. [c] Major products were (*E*)- and (*Z*)-Phenyl *β*-(trifluoromethyl)vinyl sulfides (**4a**). [d] No reaction. [e] KOH was used instead of NaH. See ref 5a.

Initially, an S_N2'-type reaction of **1** and thiophenol was examined under various reaction conditions (Table 1). When the reaction of **1** (3.0 equiv) and thiophenol (1.0 equiv) was conducted in THF in the presence of NaH (1.3 equiv), the desired S_N2'-type product **2a** was obtained along with an unexpected structural isomer **3a**, with a ratio of **2a**/**3a** = 80/20 in 57% combined yield. Although this mixture could not be separated into its components. The structures of **2a** and **3a** were assigned on the basis of their ^{1}H and ^{19}F NMR (see Supporting Information). The product **3a** was probably formed via an excessive S_N2'-type reaction of **2a** with thiophenoxide. When this reaction was carried out in 1,4-dioxane for 6 h, the selectivity was improved to give the products with a ratio of **2a**/**3a** = 93/7 in 73% combined yield. Modifications of the amount of **1** influenced the product selectivity to some extent. Reducing the amount of **1** to 1.0 equiv resulted in a slightly lower selectivity, whereas increasing the amount of **1** to 5.0 equiv resulted in the slightly higher selectivity. Interestingly, other tested solvents suppressed the formation of the desired product **2a**.

With the optimized reaction conditions in hand, the substrate scope was explored using 3.0 equiv of **1** and various thiols in the presence of NaH (1.3 equiv) at room temperature. As shown in Table 2, the reaction smoothly proceeded with a wide range of substrates, providing the corresponding S_N2'-type product **2b**–**2l** in good to high yields with high to excellent selectivities. It is noteworthy that the alkylthiols gave the corresponding S_N2'-type products exclusively, in sharp contrast to arylthiols.

Table 2. Substrate Scope of S_N2'-Type Reaction of **1**[a]



entry	R	time [h]	**2**	yield[b] [%]	**2:3**[c]
1	2,4-Me-C_6H_3	6	**2b**	84	94/6
2	$nC_{12}H_{25}$	6	**2c**	82	>99/1
3	tBu	3	**2d**	75	99/1
4	Ph_3C	3	**2e**	86	99/1
5	$PhCH_2CH_2$	18	**2f**	82	99/1
6	$PhCH_2$	3	**2g**	88	99/1
7	4-Me-$C_6H_4CH_2$	7	**2h**	78	>99/1
8	4−Cl−$C_6H_4CH_2$	7	**2i**	73	99/1
9	4-MeO-$C_6H_4CH_2$	7	**2j**	75	>99/1
10	2−Cl−$C_6H_4CH_2$	4	**2k**	79	99/1
11	2,4,6-Me-$C_6H_4CH_2$	6	**2l**	77	>99/1

[a] The reaction of **1** (3.0 equiv) with RSH (1.0 equiv) was carried out in the presence of NaH (1.3 equiv) in 1,4-dioxane at room temperature. [b] Isolated yield. [c] The ratio was determined by ^{19}F NMR spectroscopy.

These findings suggest that one factor for the occurrence of excessive S_N2'-type reaction of **2** might be associated with the pK_a value of thiols.

We then turned our attention to synthetic applications of the above products **2**. *gem*-Difluoroallenes have attracted attention due to their potential as difluorinated synthons; however the study on the facile preparation of functionalized *gem*-difluoroallenes is rare.[8] We therefore examined the synthesis of *gem*-difluoroallenyl sulfide from 2-bromo-3,3-difluoroallyl sulfide using an elimination reaction. The preliminary experiment involved the reaction of **2a** with a slight excess amount of LDA (1.2 equiv) in THF at −78 °C. This reaction resulted in the decomposition of **2a** along with recovery of the unreacted starting material **2a**, giving no desired *gem*-difluoroallenyl sulfide **5a**. Instead of **2a**, the use of **2d** also lead to a similar result. At this point, we were aware of the incomplete consumption of **2a** in spite of the excessive use of LDA. This result led us to speculate that, prior to full deprotonation of **2a** by LDA, the produced product **5a** might undergo the next deprotonation process to generate the corresponding allenyl anion which may easily decompose. On the basis of this working hypothesis, we conducted the reaction of **2a** with LDA (2.2 equiv) in the presence of an excess amount of TMSCl (5.0 equiv) in order to trap the generated allenyl anion. The expecting reaction turned out to be complicated, giving many products by GC-MS analysis.

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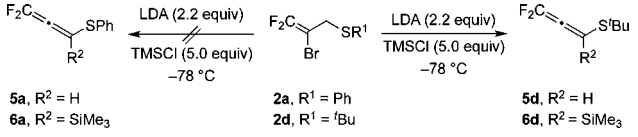
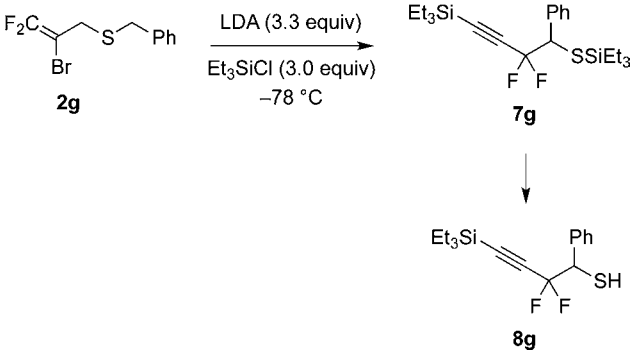
Interestingly, when the reaction of **2d** was carried out, the generation of *gem*-difluorosilylallenyl sulfide **6d** was analyzed by GC-MS. The main GC-MS peak appeared at m/z = 179 (M^+-tBu) [MW = 236 ($C_{10}H_{18}F_2SSi$)], which would suggest the structure of **6d**. After the usual workup of the reaction, the residual oil was purified by distillation to give **6d** along with a small amount of inevitable contaminants. The structure of **6d** was further confirmed by ^{19}F and ^{13}C NMR spectra. Both terminal fluorine signals appeared at −103.48 ppm (s). The central sp-carbon was observed at 165.3 ppm (t, J = 35.1 Hz), and two sp^2-carbons at two ends of the allenyl moiety appeared at 156.4 ppm (t, J = 259.3 Hz) and 134.4 ppm (t, J = 7.0 Hz) (Scheme 1). Unfortunately, purification of the product using silica gel column chromatography resulted in the decomposition of **6d** as observed by multiple peaks in GC-MS analysis.

Scheme 1. Reaction of **2a** and **2d** with LDA in the Presence of Me_3SiCl



However, to our surprise, when we carried out the reaction of **2g** with LDA (2.2 equiv) in the presence of TESCl (2.0 equiv) in THF at −78 °C for 10 min, we observed one new peak in GC-MS analysis at m/z = 397 (M^+-Et) [MW = 426 ($C_{22}H_{36}F_2SSi_2$)] which would suggest the structure of **7g** together with the unreacted **2g** (ca. 40%). No consumption of the remaining **2g** occurred during stirring at room temperature for a prolonged reaction time. For the complete consumption of **2g** we performed a similar reaction with excess LDA (3.3 equiv) in the presence of excess TESCl (3.0 equiv). The reaction cleanly proceeded to give the unexpected *gem*-difluorohomopropargyl thiol **8g** in 82% yield as a desilylated product of **7g** after silica gel column purification (Scheme 2).

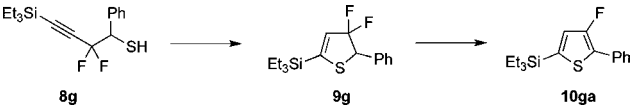
Scheme 2. Synthesis of *gem*-Difluorohomopropargyl Thiol (**8g**)



The structure of **8g** was confirmed by ^1H, ^{13}C, and ^{19}F NMR spectra and FT-IR. The methine proton signal was observed at 4.4 ppm (ddd, J = 12.3, 8.2, 6.4 Hz). Two sp-carbon signals appeared at 94.4 ppm (t, J = 4.7 Hz) and 96.1 ppm (t, J = 39.0 Hz). Two signals of the geminal fluorines were observed at −85.0 ppm (dd, J = 267.0, 8.2 Hz) and −88.0 ppm (dd, J = 267.0, 12.2 Hz). The peak at 2186 cm^{-1} in the FT-IR spectrum was assigned to CC triple bond stretching vibrations. However, this *gem*-difluorohomopropargyl thiol **8g** gradually turned yellow at room temperature after solvent removal, giving several peaks by GC-MS because of its unstable nature.

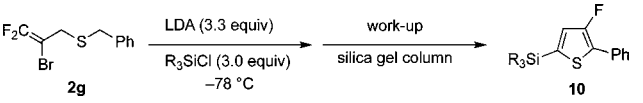
We also found further transformation of **8g** to the novel fluorinated thiophene **10ga** via the corresponding 3,3-difluorodehydrothiophene **9g** (Scheme 3).[9]

Scheme 3. Synthesis of 2-Phenyl-3-fluoro-5-triethylsilylthiophene (**10ga**)



These results prompted us to examine the overall transformation reaction from **2g** to **10ga**. Selected reaction conditions of this one-pot synthesis of 3-fluorothiophene derivative **10** are shown in Table 3.

Table 3. Screening of One-Pot Reaction Conditions of **2g**



entry	R_3SiCl	workup	additive	product	yield[a] [%]
1	Et_3SiCl	sat. $NaHCO_3$	Et_3N	**10ga**	82
2	Et_3SiCl	sat. NaCl	none	**10ga**	79
3	Et_3SiCl	sat. NaCl	Et_3N	**10ga**	83
4	Me_3SiCl	sat. NaCl	Et_3N	**10ga**	79
5	$PhMe_2SiCl$	sat. NaCl	Et_3N	**10ga**	70[b]
6	$Ph_2MeSiCl$	sat. NaCl	Et_3N	**10ga**	45[c]

[a] Isolated yield. [b] 93% purity. [c] The corresponding desilylated 3-fluorothiophene derivative was isolated in 29% yield.

After an extensive screening of reaction parameters (including chlorosilane, workup, and the additive), we identified the following three factors for generating 2-phenyl-3-fluoro-5-triethylsilylthiophene (**10ga**) in 83% chemical yield (entry 3): (1) Chlorotriethylsilane (Et_3SiCl) was

(9) The structure of **9g** was identified by ^1H and ^{19}F NMR spectra and GC-MS [m/z = 312 (6, M^+)]. The methine proton signal appeared at 5.82 (s), and the vinylic proton signal, at 4.89 (dd, J = 20.8, 17.4 Hz), respectively. Two *gem*-fluorine signals appeared at −85.0 (dd, J = 254.8, 20.8 Hz) and −86.1 (dd, J = 254.8, 17.4 Hz), respectively. This 4,4-difluoro-3,4-dihydrothiophene (**9g**) was easily transformed into **10ga** during silica gel column chromatographic purification.

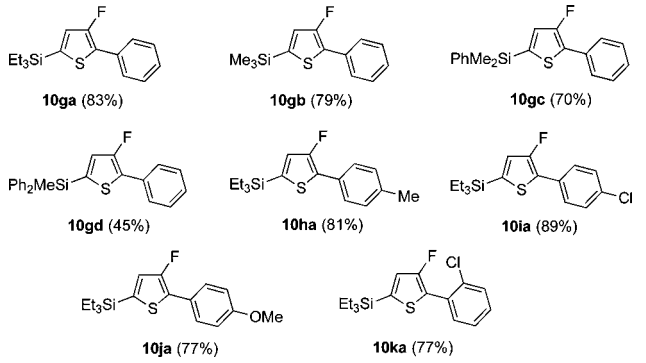


Figure 1. 2-Aryl-3-fluoro-5-triethylsilylthiophenes (**10**).

the optimal silylating agent. (2) Direct addition of aqueous sodium chloride solution to the reaction mixture at −78 °C was suitable for quenching the reaction. (3) The successive cyclization reaction was accelerated in the presence of triethylamine (see experimental details in Supporting Information). It is noteworthy that this one-pot protocol requires silica gel chromatographic purification only once.

Under the optimized reaction conditions, the scope of this one-pot 3-fluorothiophene synthesis was demonstrated with a series of 2-bromo-3,3-difluoroallyl sulfides **2f**−**2l**. When we employed the sulfides **2h**−**2k**, the reaction similarly proceeded to give the corresponding 3-fluorothiophene derivative **10ha**−**10ka** in high yields, respectively (Figure 1). In contrast, treatment of **2f** and **2l** under identical conditions did not give the desired 3-fluorothiophene derivatives but the corresponding *gem*-difluoroallene derivatives **5f** and **5l** (not shown).

With these experimental results, our plausible reaction mechanism is postulated in Scheme 4. Initially, 2-bromo-3,3-difluoroallyl benzyl sulfide (**2g**) undergoes deprotonation at the benzylic instead of the allylic position, followed by [2,3]sigmatropic rearrangement to form the corresponding *gem*-difluorohomopropargyl thiolate **B**.[10] After the formation of the silylated product **C**, although such intermediates have not been observed, the bromoethylene moiety was transformed into the terminal acetylene by LDA followed by silylation at the terminal carbon to yield the product (**7g**). Desilylation of **7g** proceeds, giving the free *gem*-difluorohomopropargyl thiol (**8g**)

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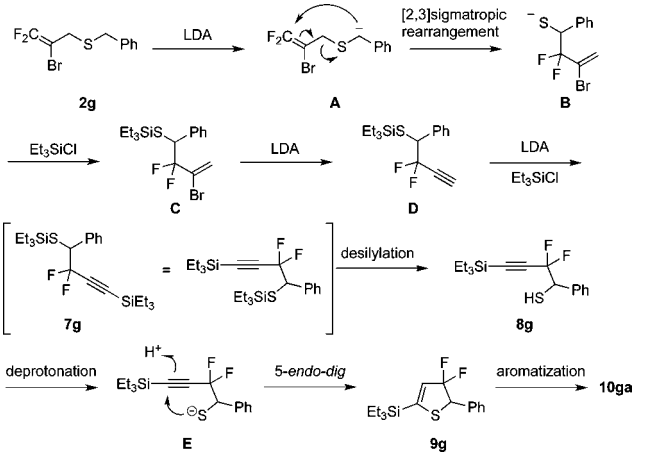
Scheme 4. Plausible Mechanism for 3-Fluorothiophene Formation



under basic aqueous conditions, which undergoes similar intramolecular cyclization in a 5-*endodig* fashion, as reported by Hammond.[11] Finally, the resulting 4,4-difluoro-3,4-dihydrothiophene (**9g**) easily undergoes aromatization on the silica gel column chromatography yielding the 3-fluorothiophene **10ga**.

In conclusion, we have developed the first successful S_N2'-type reaction of 2-bromo-3,3,3-trifluoropropene (**1**) and various thiols. The reaction provides the corresponding 2-bromo-3,3-difluoroallyl sulfides (**2**) in good to high yields with high to excellent selectivities. The resulting 2-bromo-3,3-difluoroallyl benzyl sulfides are then efficiently transformed into the novel 2-aryl-3-fluoro-5-triethylsilylthiophenes (**10**) in high yields. Studies on related synthetic transformations of 3-fluorothiophene (**10**) and the alternative synthetic use of 2-bromo-3,3-difluoroallyl sulfides (**2**) are in progress in our laboratory.

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Supporting Information Available. Experimental procedure and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.