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Property and Reactivity of Fluoro(silyl)acetylenes and Fluoro(stannyl)acetylenes

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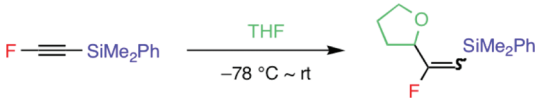
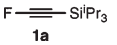


Fluoro(silyl)acetylenes and fluoro(stannyl)acetylenes underwent a radical addition reaction of THF to furnish the corresponding fluorinated cyclic ethers in moderate to good yields. These intriguing addition reaction proved to proceed via a radical reaction mechanism.

Fluorinated organic molecules would be one of the most important classes of halogenated compounds with rare occurrence in nature.[1] They often play a significant role in the modern drug discovery process, which should make the development of new synthetic methodologies to facilitate their preparation worthwhile.[2] Therefore, a number of methods have been reported to synthesize a variety of fluoroalkanes, fluoroalkenes, and fluoroarenes due to their useful applications. In contrast to such main stream, study on fluoroalkyne chemistry has lagged far behind.[3] One of the reasons may be attributed to the instability and explosive nature of fluoroacetylenes in previous reports.[4] We have recently undertaken studies aimed at such a fluoroacetylene family and reported a synthetic method for the facile preparation of fluoro(triisopropylsilyl)acetylene **1a**.[5] As we noticed that **1a** turned out to be stable only in a hexane solution at low temperature, its further synthetic applications remained unexplored. After we started to investigate the properties and reactivity of fluoro(silyl)acetylenes, we successfully isolated fluoro(triisopropylsilyl)acetylene **1a** in the pure form and measured its ^{13}C NMR for the first time. In addition, we serendipitously encountered the addition reaction of THF to other analogous fluoro(silyl)acetylenes and fluoro(stannyl)acetylenes except for **1a**. In this paper, we disclose an intriguing behavior of fluoro(silyl)acetylenes and fluoro(stannyl)acetylenes and propose the possible reaction mechanism of the fluorinated cyclic ethers.

Although we have previously established the facile preparation of **1a** from 1,1-difluoroethylene, the fluoroacetylene was only stable in a hexane solution. Thus, concentration of the hexane solution containing **1a** resulted in the decomposition of **1a**. However, the different perspective for this outcome provided us a hint that hexane as a solvent might be responsible for stabilization of **1a**. On the basis of this idea we carried out purification of **1a** through distillation from the corresponding hexadecane solution containing **1a** (we confirmed that hexadecane has a higher boiling point in comparison with that of **1a** by GC-MS in advance) using a short path distillation apparatus. We determined that the desired acetylene **1a** was successfully distilled at 30−35 °C (bath temperature) at 40 Pa as a colorless oil. To our delight, the isolated compound **1a** was stable enough to execute the following measurement. We immediately attempted to measure the ^{13}C NMR spectrum of **1a**. Although **1a** in $CDCl_3$ started slowly to decompose at −10 °C, over ten accumulation times we were able to perform the ^{13}C NMR measurement without any detectable decomposition of **1a**. The ^{13}C NMR spectrum of **1a** is shown in Figure 1.



1a

Interestingly, one acetylene carbon signal appeared at 19.09 ppm (d, $J = 17.4$ Hz) and the other signal appeared at 106.91 ppm (d, $J = 337.6$ Hz). On the basis of the coupling constant of carbon atom−fluorine atom, the former was assigned to the sp-carbon attached to silicon and the latter was assigned to the sp-carbon attached to fluorine. Although we did not have any rational reason to explain these two sp-carbon chemical shifts at the present stage, this is the first ^{13}C NMR spectrum observation of sp-carbon attached directly to fluorine. In addition, the elemental analysis of **1a** was successfully conducted to give satisfactory results (elemental analysis calcd for $C_{11}H_{21}FSi$: C 65.94, H 10.56; found: C 66.19, H 10.82) for the first time, although exposure of the colorless oil **1a** to air resulted in coloration to the pale yellow oil.

To assist the interpretation of the unexpected chemical shift values shown above, we have conducted quantum

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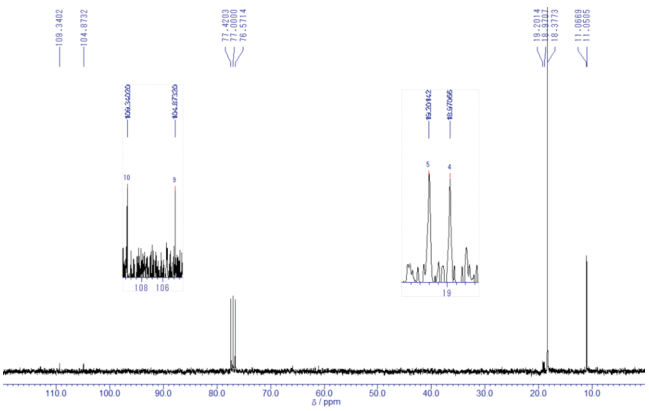


FIGURE 1. ^{13}C NMR of **1a**.

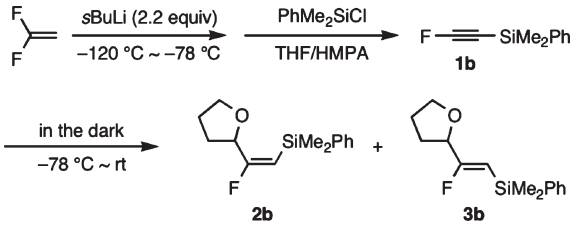
TABLE 1. ^{13}C NMR Chemical Shifts (ppm) for sp-Carbon Atoms

	δC1	δC2
exptl	106.9	19.1
HF	115.8	17.0
MP2	111.8	17.2
B3LYP	119.1	16.4

chemical calculations for **1a** using Gaussian03.[6] Geometry optimizations were performed at the B3LYP/6-31G** level, and the optimized structures were used for the subsequent calculations of molecular properties. The GIAO nuclear magnetic shielding values were calculated at all atomic positions at the HF, MP2, and B3LYP levels of theory using the 6-311+G(2d,p) basis set. The chemical shifts for the carbon atoms were obtained by subtracting their chemical shielding values from the one calculated for TMS, which is 192.6, 192.9, or 182.8 ppm for HF, MP2, or B3LYP, respectively. Table 1 summarizes the observed and calculated chemical shifts for the sp-carbon atoms. As shown in the table, the present quantum chemical calculations reproduce the observed chemical shifts.

We turned our attention to substrate scope and chose fluoro(dimethylphenylsilyl)acetylene **1b** as an analogous molecule of **1a**. We attempted to prepare **1b** in the similar manner. After complete addition of the components at −78 °C, the reaction mixture was allowed to stand at room temperature overnight under exclusion of light.[7] At this time we encountered the following unexpected finding. When we checked the reaction progress by GC−MS analysis prior to quench, the original peak corresponding to **1b** [m/z 163 ($M^+ - Me$), M = 178 ($C_{10}H_{11}FSi$)] almost disappeared and

SCHEME 1. Synthesis of 2b and 3b



a new major peak emerged at m/z 234 along with minor peaks. After the usual workup, the residual oil was separated by silica gel column chromatography to afford the corresponding products. The main product showed one vinyl proton signal at 5.07 ppm (δ, J = 34.1 Hz) in the ^1H NMR spectrum, one vinyl fluorine signal at −85.9 ppm (dd, J = 33.9, 24.2 Hz) in the ^{19}F NMR spectrum, and two vinyl carbon signals at 99.7 (d, J = 3.1 Hz) and 167.69 ppm (d, J = 279.6 Hz) in the ^{13}C NMR spectrum, respectively. On the basis of these NMR data, this molecule was assigned to be (*E*)-[2-fluoro-2-(tetrahydrofuran-2′-yl)vinyl]dimethylphenylsilane **2b**.[8] On the other hand, the minor (*Z*)-isomer **3b** showed one vinyl proton signal at 4.96 ppm (d, J = 61.7 Hz) in the ^1H NMR spectrum and one vinyl fluorine signal at −95.0 ppm (dd, J = 62.0, 8.9 Hz) in the ^{19}F NMR spectrum. The characteristic H−F coupling constant of each stereoisomer justified the structural assignment. The *E*/*Z* ratio of the stereoisomers (**2b**/**3b**) was determined to be 86:14 by GC−MS analysis, using a crude reaction mixture prior to chromatographic purification (Scheme 1).

These unexpected results prompted us to examine substrate scope. Various chlorosilanes and chlorostannanes were subjected to investigation. Although the addition reactions proceeded giving the corresponding adducts **2c**−**h**, the yields were generally modest under similar conditions [Table 2, Method A (left column)]. Interestingly, sterically demanding chlorotriphenylsilane scarcely underwent the first substitution reaction of lithium fluoroacetylide with the result that a trace amount of the corresponding adduct was detected by GC-MS (entry 6). These unsatisfactory results led us to reexamine the reaction conditions for the preparation of **2b**. After many attempts,[9] we eventually found that the key factor contributing to higher yield probably depended on the reaction concentration. Thus, after the complete generation of **1b** at −78 °C was confirmed, the reaction mixture was gradually warmed to −40 °C. At this temperature, an excessive amount of THF was carefully added to the mixture. This diluted reaction mixture was gradually warmed to room temperature while being stirred, which resulted in acceptable yield (up to 78%). Once the optimum reaction conditions had been identified, the remaining substrates were again subjected to examination. All of the reactions proceeded well with moderate to high yields [Table 2, Method B (right column)]. Although the yields were improved in this way in almost every case, the problem of stereoselectivity still remains unsolved. To gain the reaction progress in detail we monitored the reaction of **1b** with the reaction temperature by GC−MS analysis. The first appearance of the peak **2b**

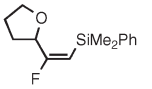
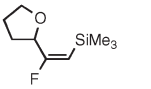
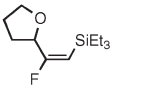
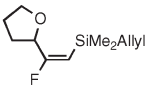
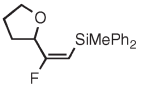
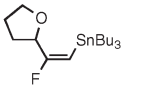
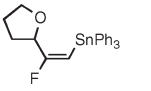
(6) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, Revision A.2; Gaussian, Inc., Wallingford CT, 2009.

(7) The same reaction in the light caused formation of unidentified byproduct and decreased the yield of **2b**.

(8) Muramatsu, H.; Inukai, K.; Iwata, Y.; Murakami, S. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 1284.

(9) Use of THF as a solvent is essential to successful preparation of fluoro(silyl)acetylene.

TABLE 2. Reaction of Fluoro(silyl)acetylene and Fluoro(stannyl)acetylene

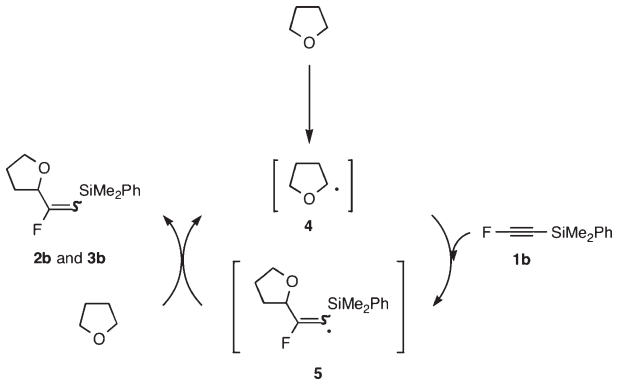
entry	electrophile	major product		yield (%)[a] (E:Z)[b]	
				method A[c,d]	method B[e]
1	$PhMe_2SiCl$		**2b**	52 (86:14)	78 (82:18)[f]
2	Me_3SiCl		**2c**	41 (74:26)	95 (65:35)[g]
3	Et_3SiCl		**2d**	18 (76:24)[h]	33 (76:24)[g,h]
4	$AllylMe_2SiCl$		**2e**	27 (75:25)	52 (60:40)[g]
5	$Ph_2MeSiCl$		**2f**	41 (79:21)	77 (82:18)[f]
6	Ph_3SiCl	Complex mixture	**2g**	0[i]	——
7	Bu_3SnCl		**2h**	21 (66:34)	52 (74:26)[g]
8	Ph_3SnCl		**2i**	——	41 (80:20)[f]

[a]Isolated yield. [b]Determined by GC-MS analysis in the crude reaction mixture otherwise noted. [c]Under the preliminary reaction conditions. [d]Reaction concentration (0.17 M). [e]Under the optimized reaction conditions. [f]Reaction concentration (0.10 M). [g]Reaction concentration (0.07 M). [h]Determined by NMR after column chromatography. [i]The corresponding fluoro(triphenylsilyl)acetylene was scarcely detected by GC-MS analysis.

along with **1b** was observed at around −20 °C. Thus, **1b** remained intact in THF at least below ca. −30 °C, and was subjected to the addition reaction of THF at ca. −20 °C, giving **2b** and **2c**.

Our next task is to clarify whether this reaction proceeded via an ionic or a radical process. We conducted the following two reactions under different conditions. Thus, after preparing **1b** at −78 °C again, first we slowly added an excessive amount of THF (5 mL) and water (10 equiv to **1b**) to this solution at −40 °C. The mixture was gradually warmed to room temperature after the complete addition. In this case, the addition reaction smoothly proceeded to afford the corresponding products **2b** and **3b** in essentially the same manner [82%, **2b**:**3b** = 81:19, compare to entry 1 (Method B) in Table 1 (78%, **2b**:**3b** = 82:18)]. On the other hand, after preparing **1b** at −78 °C, the addition of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO, 1.1 equiv to **1b**) instead of water at the same time completely retarded the addition reaction to afford no THF adducts at −20 °C. Moreover, even at room temperature, the peak of **1b** was observed essentially intact by GC−MS in the reaction mixture for a short time. TEMPO gradually decomposed at this temperature under these conditions, which may cause decomposition of **1b**, finally giving the complex reaction mixtures. Surprisingly, even at the final stage no formation of **2b** and **3b** was detected in the complex mixtures by GC-MS.

SCHEME 2. Plausible Reaction Mechanism



Furthermore, EPR studies of the reaction were briefly attempted to confirm its radical mechanism. We monitored the EPR spectra of the reaction solution containing **1b** and 5,5-dimethyl-1-pyroline *N*-oxide (DMPO) as a radical trap reagent with the reaction temperature. We observed the multiplet line with a *g* value of 2.0066, which corresponded to 5,5-dimethyl-2-substituted-1-pyrrolidine *N*-oxide radical. These peaks corresponded to the triplet hyperfine structure by an N nuclei ($I = 1$) and the doublet hyperfine structure by one adjacent H nuclei ($I = 1/2$). The former hyperfine coupling constant (A_N) was 1.38 mT and the latter one (A_H) was 1.72 mT. However, no further information about the substituent at the 2-position on the pyrrolidine ring was obtained under our experimental conditions.

On the basis of these results and previous findings in another group,[10] our proposed radical mechanism is shown in Scheme 2. Initially, a trace amount of inevitable and/or adventitious oxygen generated the corresponding THF radical **4**. The radical **4** almost regioselectively attacked at the β-carbon of **1b** to yield the corresponding fluorovinyl radical **5**. The radical **5** abstracted the α-hydrogen of THF to afford the products (**2b** and **3b**) and to regenerate the THF radical **4**. As the result, the complete radical cycle mechanism should be successfully accomplished. In summary, we have demonstrated fluoro(triisopropylsilyl)acetylene **1a** and the first successful ^{13}C NMR measurement of the radical reaction of fluoro(silyl)acetylenes (**1b**−**f**) and fluoro(stannyl)-acetylenes (**1h** and **1i**) with THF. We also have verified the stability of these fluoro(silyl)acetylenes and fluoro(stannyl)-acetylenes in THF in the absence of oxygen. Although their final decomposition mechanism is not clear at the present stage, these findings would contribute a new aspect of fluoroacetylene chemistry.

Experimental Section

[2-Fluoro-2-(tetrahydrofuran-2′-yl)vinyl]dimethylphenylsilane (2b and 3b). A 25-mL two-necked flask equipped with a magnetic stir bar, a stopcock, and a three-way stopcock was charged with 2.5 mL of THF under argon. To this solution was added *s*BuLi (1.04 M in cyclohexane−hexane solution, 1.4 mL, 1.46 mmol, 2.2 equiv) dropwise via syringe at −78 °C. After being stirred for

(10) Bergstrom, D. E.; Ng, M. W.; Wong, J. *J. Chem. Soc., Perkin Trans. 1* **1983**, 741.

an additional 5 min, the solution was cooled to −120 °C via liquid N_2/ethanol bath. At this temperature, argon was replaced with 1,1-difluoroethylene (balloon). The mixture was gradually warmed to −85 °C. HMPA (6.0 μL, 5 mol %) at −85 °C and chlorodimethylphenylsilane (110 μL, 0.67 mmol) at −78 °C were successively added to the solution via syringe. After the mixture was stirred for 10 min, the reaction flask was covered with aluminum foil. The mixture was slowly warmed to −40 °C while an excess amount of 1,1-difluoroethylene was gradually let out through the drying glass tube filled with calcium chloride. When the reaction mixture reached −40 °C, the additional THF (5.0 mL) was carefully added to the solution. After removal of the cooling bath at −30 °C, the reaction mixture was allowed to stand overnight. To the resulting solution was carefully added hexane and water, successively. After the resultant mixture was extracted with hexane, additional extraction was repeated twice. The combined solution was dried over sodium sulfate. The solution was concentrated in vacuo and the residual oil was quickly purified by chromatography on a short silica gel column covered with aluminum foil (hexane:ethyl acetate:triethylamine = 200:4:1 as an eluent) to give a mixture of **2b** and **3b** [78% (130.7 mg), E/Z = 82:18]. The pure sample **2b** was obtained even at the expense of the yield from partial fractions by the second chromatography on longer silica gel column of the mixture of **2b** and **3b** under the same separation conditions. **2b**: R_f 0.49; hexane:ethyl acetate:triethylamine = 200:4:1; elemental analysis calcd for $C_{14}H_{19}FOSi$: C 67.16, H 7.65; found: C 67.19, H 7.69; δ_H = 0.40 (3H, s), 0.42 (3H, s), 1.70−2.00 (4H, m), 3.65−3.90 (2H, m), 4.43 (1H, dt, J_{HF} = 25.0 Hz, J_{HH} = 7.3 Hz), 5.07 (1H, d, J_{HF} = 34.1 Hz), 7.30−7.50 (5H, m) ppm; δ_F = −85.9 (dd, J_{FH} = 34.1, 25.0 Hz) ppm; δ_C = −0.86 (d, J_{CF} = 1.9 Hz), −0.69 (d, J_{CF} = 1.9 Hz), 26.3 (s), 29.2 (s), 69.2 (s), 76.1 (d, J_{CF} = 32.4 Hz), 99.7 (d, J_{CF} = 3.1 Hz), 127.9 (s), 129.2 (s), 133.6 (s), 138.5 (d, J_{CF} = 1.9 Hz), 167.7 (d, J_{CF} = 279.6 Hz) ppm; ν = 3069, 2956, 2873, 1652, 1429, 1112, 1059, 791, 700 cm^{-1}; GC-MS (m/z) 235 [M^+ − 15 (Me), 47], 193 (46), 155 (8), 129 (76), 105 (23), 77 (100), 53 (16). **3b**: R_f 0.30; hexane:ethyl acetate:triethylamine = 200:4:1; δ_H = 0.40 (3H, s), 0.41 (3H, s), 1.85−2.16 (4H, m), 3.80−4.00 (2H, m), 4.39 (1H, dt, J_{HF} = 8.3 Hz, J_{HH} = 4.8 Hz), 4.96 (1H, d, J_{HF} = 61.7 Hz), 7.30−7.50 (5H, m) ppm; δ_F = −95.0 (dd, J_{FH} = 61.7, 8.3 Hz) ppm; ν = 3071, 2957, 1662, 1428, 1249, 1114, 1078, 1060, 834, 731, 699 cm^{-1}; GC-MS (m/z) 235 [M^+ − 15 (Me), 0.9], 173 (4), 139 (100), 129 (60), 91 (65), 79 (42), 77 (84).

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Supporting Information Available: Characterization of new compounds **2c**−**i**, and NMR spectral for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.