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Functionalization of Monofluoroallene and the Synthesis of Aryl-Substituted Conjugated Fluorodienes

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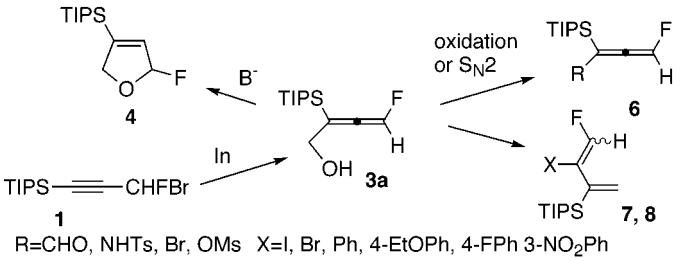
ABSTRACT



4-Fluoroallenol 3a, prepared from 1, cyclized easily to 4 but preserved its fluoroallenyl integrity under oxidation and S_N2 displacement to yield aldehyde, amine, mesylate, and halide 6. Allylic isomerization yielded 2-halo-1-fluoro-1,3-butadiene 7, which underwent a Suzuki coupling to give aryl-substituted conjugated diene 8.

Fluorinated allenes blend the unique stereoelectronic properties of fluorine with the well-known synthetic capabilities of the allene moiety. This unique combination makes them attractive building blocks for the synthesis of partially fluorinated alicyclic compounds not accessible through current fluorinating strategies. Their ring-forming capability was showcased in our recently published regiospecific synthesis of bicyclo- and heterobicyclo-*gem*-difluorocyclobutene, via a novel Mo-catalyzed intramolecular [2 + 2] cycloaddition of a functionalized *gem*-difluoroallene.[1] In theory, a suitably functionalized monofluoroallene could also be used to construct alicyclic monofluoro compounds. This potential—first recognized by Dolbier[2]—has not prospered further because synthetic routes to substituted monofluoroallenes are painstakingly few. One such preparation involved treating acetylenic alcohols with sulfur tetrafluoride.[3] Later, Castelhano and Krantz introduced the only other viable route: reduction of a fluorochloropropargyl precursor with aluminum hydride.[4] We now report a practical, environmentally benign synthesis of fluoroallenyl alcohol **3a**, its cyclization to fluorodihydrofuran **4**, and its functional group interconversion to fluoroallenyl derivatives with desirable synthetic handles—suitable for chain extension or further functionalization—such as aldehyde, amine, mesylate and halide **6**, and diene **7**. The latter furnished 2-aryl-substituted 1,3-dienes **8** via Suzuki coupling.

Our group has reported the preparation of difluoroallenyl indium **2b**, in predominantly aqueous media (Scheme 1), and its reaction with formaldehyde to yield allenyl alcohol **3b**.[5] This discovery encouraged us to investigate whether a monofluorinated allenyl indium analogue **2a** could be similarly prepared from bromofluoropropyne **1a**. Although we could not isolate **2a** using the same conditions as for **2b**, proof of its fleeting existence was the formation of TIPS-

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(1) Shen, Q.; Hammond, G. B. *J. Am. Chem. Soc.* **2002**, *124*, 6534−6535.
(2) Dolbier, W. R., Jr. *Acc. Chem. Res.* **1991**, *24*, 63−69.
(3) Dear, R. E.; Gilbert, E. E. *J. Org. Chem.* **1968**, *33*, 819−823.
(4) Castelhano, A. L.; Krantz, A. *J. Am. Chem. Soc.* **1987**, *109*, 3491−3493.
(5) Wang, Z.; Hammond, G. B. *J. Org. Chem.* **2000**, *65*, 6547−6552.

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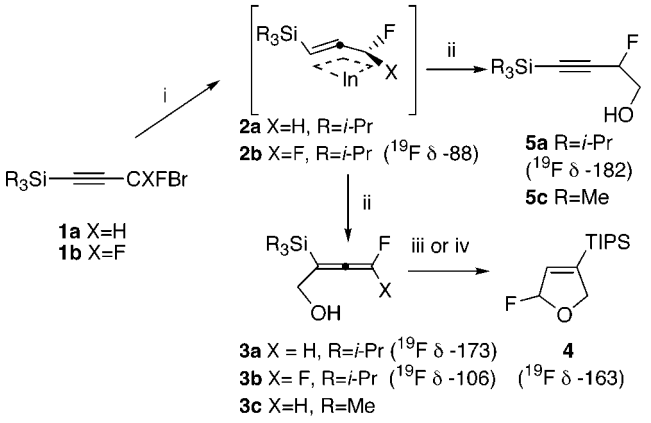
Scheme 1. Synthesis and Cyclization of Fluoroallenol **3b**[a]

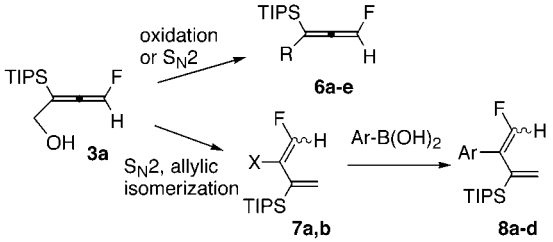


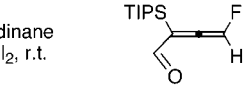
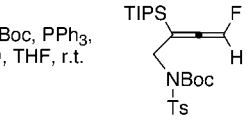
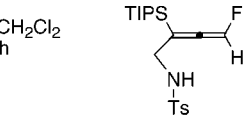
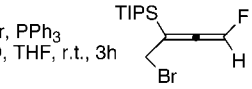
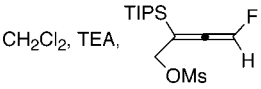
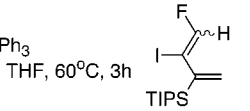
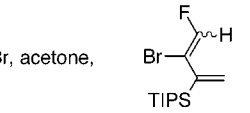
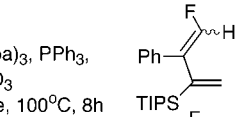
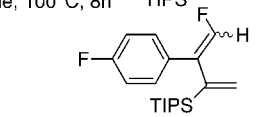
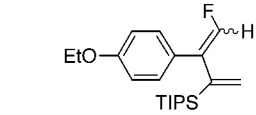
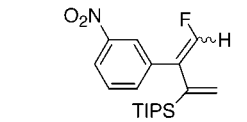
[a] Key: (i) In (1 equiv); (ii) **3a**, $HCHO_{aq}$, (5 equiv), THF, rt (66%); (iii) TBAF, THF, −80 °C, 15 min (62%); (iv) NaH, THF, rt, 2 h (75%).

CH═C═CHF, accompanied by its propargylic isomer (1:1 ratio) and unreacted starting material. By eliminating water as cosolvent in the reaction and trapping **2a** with an excess of aqueous formaldehyde, we obtained the desired **3a**, this time accompanied by **5a** in a 7:1 ratio. The allene/propargyl ratio was reversed when TIPS was replaced with TMS to give a mixture of **5c**/**3c** (2:1). In both cases, the only other byproduct was the dimer $(R_3SiC{\equiv}CCHF)_2$, easily separated by chromatography because of its very low polarity. With an expedient synthesis of **3a** in hand, we proceeded to study its chemistry. An attempted TBAF desilylation afforded dihydrofuran **4**, in 62% yield, by means of a 5-*endo*-*trig* cyclization path. The same product could be isolated in better yield using sodium hydride.[6] A plausible reaction mechanism involves the nucleophilic attack by oxygen on the distal double bond of the allene, generating a negative charge on the ring that is stabilized by a favorable β-effect of the silicon atom.[5] In contrast, the Ag(I)-catalyzed cyclization[7] of **3a** resulted in the elimination of fluoride and the formation of 3-TIPS-furan (65%). Similarly, when **3a** reacted with iodine in THF at rt, the loss of fluoride was accompanied by iodo substitution to give 3-TIPS-4-iodofuran (60% yield).

To find out if a functional group interconversion in **3a** could be carried out without compromising the integrity of the fluoroallenyl moiety, we first probed the alcohol to aldehyde oxidation in **3a**. This oxidation, using Dess−Martin[8] conditions, resulted in a facile synthesis of **6a** in very good yield (entry 1, Table 1). Another functional group interconversion, the replacement of O by N in **3a**, was carried out in high yield under Mitsunobu[9] conditions with *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide (entry 2). Removal of the BOC-protecting group in **6b** afforded **6c** (entry 3). Its

Table 1. Chemical Modifications Derived from **3a**



entry	method	product	yield[a]	^{19}F δ (ppm)[b]
1	Periodinane CH_2Cl_2, r.t.		**6a** (83%)	-180.5
2	HNTsBoc, PPh_3, DEAD, THF, r.t.		**6b** (83%)	-173
3	TFA, CH_2Cl_2 r.t., 2h		**6c** (76%)	-172
4	*n*-PrBr, PPh_3 DEAD, THF, r.t., 3h		**6d** (42%)	-175.6
5	MsCl, CH_2Cl_2, TEA, 0°C		**6e** (60%)[c]	-176
6	MeI, PPh_3 DEAD, THF, 60°C, 3h		**7a** (74%)	-95 -97
7	**6e**, LiBr, acetone, r.t., 5h		**7b**/**6d** (80%) (3:1)	-115.2 -114.6
8	$Pd_2(dba)_3$, PPh_3, Na_2CO_3 toluene, 100°C, 8h		**8a** (85%)	-132
			**8b** (70%)	-114 -132
			**8c** (77%)	-133
			**8d** (54%)	-129

[a] Isolated yield, not optimized. [b] $CFCl_3$ used as external reference; $CDCl_3$ used as solvent. [c] Used without further purification in entry 7.

recrystallization from hexane afforded X-ray quality crystals[10] that provided the first crystallographic analysis of a monofluorinated allene.[11] The integrity of the fluoroallenyl moiety

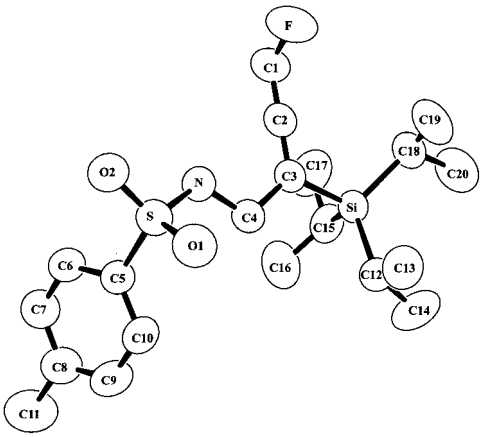
(6) Yamazaki, T.; Hiraoka, S.; Sakamoto, J.; Kitazume, T. *J. Phys. Chem. A* **1999**, *103*, 6820−6824. Ichikawa, J.; Fujiwara, M.; Wada, Y.; Okauchi, T.; Minami, T. *J. Chem. Soc., Chem. Commun.* **2000**, 1887−1888.
(7) Marshall, J. A.; Wang, X. *J. Org. Chem.* **1991**, *56*, 4913−4918.
(8) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287.
(9) Hughes, D. L. *Org. React.* **1992**, *42*, 335.

was also maintained under bromination and mesylation[12] conditions, although the resulting products **6d** and **6e**, respectively, were obtained only in moderate to good yields (entries 4 and 5).

Interestingly, one sees allylic isomerization under certain conditions. For example, treatment of **3a** with methyl iodide and Mitsunobu conditions produced the conjugated diene isomer **7a** (entry 6). Our hypothesis that an allene-containing allylic halide (4-iodo-1,2-diene) (**6**, R = CH_2I) was generated first via an S_N2 mechanism but isomerized later to the thermodynamically more stable 2-iodo-1,3-diene **7a** was confirmed by monitoring the progress of the reaction using ^{19}F NMR. At room temperature, after a reaction time of only 5 min, the signal corresponding to the starting material (δ −173) had decreased dramatically, and a new signal at δ −176 ppm, believed to correspond to the 4-iodo-1,2-diene, was observed, accompanied by two smaller signals of similar intensity at δ −95 and −97, thought to correspond to *E*/*Z* diastereomers of **7a**.

As the reaction time lengthened, the intensity of the ^{19}F signals at δ −95 and −97 increased, while the δ −176 signal decreased until its complete disappearance. The final signal ratio of δ −95 to −97 was approximately 6:1. Decreasing the temperature slowed the rate of isomerization, yet the reaction did not take place at −78 °C. Alternatively, under Finkelstein conditions (entry 7), a bromide attack on mesylate **6e** produced a mixture of diene **7b** and allene **6d** in 3:1 ratio. The fact that **6d** was still present at the end of the reaction discarded the possibility of a S_N2' allylic transposition, suggesting instead an apparent S_N2 course, followed by partial allylic isomerization, as in **7a**.

(10) ORTEP view of **6c**:



(11) For an analysis of bond lengths and angles in fluorinated allenes, see: Dixon, D.; Smart, B. *J. Phys. Chem.* **1989**, *93*, 7772−7780.

(12) A similar but higher yielding S_N2 mesylation was observed with **3b**. See: Shen, Q.; Hammond, G. B. *Org. Lett.* **2001**, *3*, 2213−2215.

1-Fluoro-1,3-butadiene has been extensively studied for conformational stability,[13] spectral characteristics,[14] reactivity in Diels−Alder reaction,[15] and [2 + 2] cycloaddition.[16] Its substituted derivatives are less known, perhaps due to their laborious synthesis. Our recent Pd-catalyzed preparation of 2-aryl- and 2-alkynyl-substituted 1,1-difluoro-1,3-butadienes[12] persuaded us to conduct a similar study with monofluorovinyl iodide **7a**. To our satisfaction, coupling **7a** with aryl boronic acids under Suzuki conditions afforded substituted-1,3-butadienes **8a**−**d** (entry 8), mostly in good or very good yields, except when a strong electron-withdrawing substituent was employed (**8d**). We have not succeeded yet at elucidating the stereochemistry of the fluorine-containing double bond in **8**—either by scalar coupling analysis or NOE experiments. Investigation is ongoing. The spectral data of **8a**−**d** showed that in each case the chemical shifts of C-1 and H-1, as well as $^1J_{HF}$ and $^1J_{CF}$ coupling constants, were in good agreement with the reported values for *E*/*Z* 1-fluoro-1,3-butadiene.[16] The chemical shift of C-4 was assigned on the basis of a DEPT experiment, but the ^{13}C NMR signals of C-2 and C-3 are interchangeable with the quaternary carbon of the aromatic ring bonded to the diene moiety.

In sum, we have found a practical preparation of fluoroallenyl alcohol **3a** and its derivatives such as aldehydes, amines, halides, and aryl-substituted conjugated dienes. Their chain extension reactions and metal-mediated cyclizations are under study.

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Supporting Information Available: Experimental procedures and spectroscopic and analytical data for **3a**−**8** and CIF files for **6c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Apeloig, Y.; Matzner, E. *J. Am. Chem. Soc.* **1995**, *117*, 5375−5376. Imade, M.; Hirao, H.; Omoto, K.; Fujimoto, H. *J. Org. Chem.* **1999**, *64*, 6697−6701.

(16) Dolbier, W. R., Jr.; Gray, T. A.; Keaffaber, J. J.; Celewicz, L.; Koroniak, H. *J. Am. Chem. Soc.* **1990**, *112*, 363−367.