

Electrophilic Fluorodesilylation of Allenylmethylsilanes: A Novel Entry to 2-Fluoro-1,3-dienes

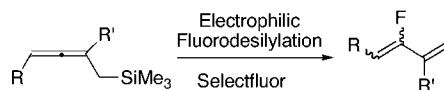
M^a Carmen Pacheco and Véronique Gouverneur*

University of Oxford, Chemistry Research Laboratory,
Mansfield Road, OX1 3TA Oxford, UK

veronique.gouverneur@chem.ox.ac.uk

Received December 29, 2004

ABSTRACT



Various fluorodienes were prepared by treatment of the corresponding allenylmethylsilanes with Selectfluor. This is the first route to these compounds not based on the use of a fluorinated building block. The reaction allows the preparation of 2-fluoro-1,3-dienes with several substitution patterns, including di- and trisubstituted compounds.

Silicon-containing π -nucleophiles are extremely valuable synthetic intermediates, reacting with electrophiles in an S_E2' fashion to give structurally diverse products.¹ In these reactions, the silyl group enhances the reactivity of the π -nucleophile and controls the sense of regiocontrol upon addition of the electrophile. In addition to allylsilanes² and allenylsilanes³ acting as allylic and propargylic transfer reagents, respectively, the S_E2' reaction of allenylmethylsilane has been used for the introduction of 1,3-dienyl-2-yl groups onto electrophiles such as aldehydes, acetals, and iminiums and also in [2 + 2] cycloadditions.⁴ These substrates have also been converted into the corresponding

bromo- or iododienes upon addition of bromine or iodine, followed by treatment with tetrabutylammonium fluoride.⁵ To the best of our knowledge, the reactivity of allenylmethylsilanes in the presence of electrophilic fluorinating reagents has not been studied. As part of our research program aimed at developing novel synthetic methodologies for the preparation of fluorinated compounds, we have reported that vinylsilanes and allylsilanes react with 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate), a reagent called Selectfluor, to give structurally diverse fluorinated compounds such as fluoroalkenes, difluorinated amides, ethers, or alcohols, as well as allylic fluorides.⁶ In this context, we became interested in the development of a novel reaction for the preparation of fluorinated dienes according to a protocol featuring the introduction of the fluorine as the very last step of a synthetic sequence. We report in this Communication an additional application of the concept of electrophilic fluorodesilylation,

(1) (a) Buckle, M. J. C.; Fleming, I.; Gil, S.; Pang, K. L. C. *Org. Biomol. Chem.* **2004**, *2*, 749–769. (b) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063–2192. (c) Betson, M. S.; Fleming, I.; Ouzman, J. V. *A. Org. Biomol. Chem.* **2003**, *1*, 4017–4024.

(2) Chabaud, L.; James, P.; Landais, Y. *Eur. J. Org. Chem.* **2004**, *15*, 3173–3199.

(3) (a) Marshall, J. A.; Maxson, K. J. *Org. Chem.* **2000**, *65*, 630–633. (b) Pomet, J. *Sci. Synth.* **2002**, *4*, 669–683. (c) Buckle, M. J.; Fleming, I. *Tetrahedron Lett.* **1993**, *34*, 2383–2386. (d) Weinreb, S. M.; Smith, D. T.; Jin, J. *Synthesis* **1998**, 509–521. (e) Han, J. W.; Tokunaga, N.; Hayashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 12915–12916.

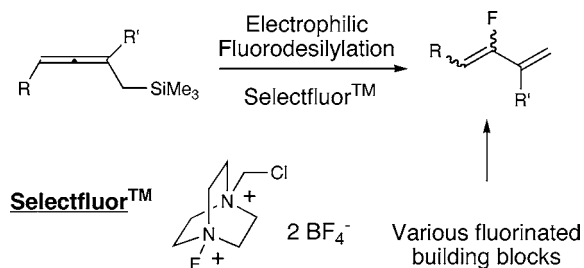
(4) (a) Ogasawara, M.; Ueyama, K.; Nagano, T.; Mizuhata, Y.; Hayashi, T. *Org. Lett.* **2003**, *5*, 217–219. (b) Mentink, G.; van Maarseveen, J. H.; Hiemstra, H. *Org. Lett.* **2002**, *4*, 3497–3500. (c) Yu, C.-M.; Yoon, S.-K.; Lee, S.-J.; Lee, J.-Y.; Kim, S. S. *Chem. Commun.* **1998**, 2749–2750. (d) Hojo, M.; Murakami, C.; Nakamura, S.; Hosomi, A. *Chem. Lett.* **1998**, 331–332. (e) Hojo, M.; Murakami, C.; Aihara, H.; Tomita, K.; Miura, K.; Hosomi, A. *J. Organomet. Chem.* **1995**, *499*, 155–157. (f) Trost, B. M.; Urabe, H. *J. Am. Chem. Soc.* **1990**, *112*, 4982–4983. (g) Colvin, E. W.; Monteith, M. J. *Chem. Soc., Chem. Commun.* **1990**, 1230–1232.

(5) (a) Hatakeyama, S.; Sugawara, K.; Takano, S. *J. Chem. Soc., Chem. Commun.* **1993**, 125–127. (b) Nishiyama, T.; Esumi, T.; Iwabuchi, Y.; Irie, H.; Hatakeyama, S. *Tetrahedron Lett.* **1998**, *39*, 43–46. (c) Yu, C.-M.; Yoon, S.-K.; Lee, S.-J.; Lee, J.-Y.; Kim, S. S. *Chem. Commun.* **1998**, *24*, 2749–2750.

(6) (a) Gouverneur, V.; Greedy, B. *Chem. Eur. J.* **2002**, *8*, 766–771. (b) Greedy, B.; Gouverneur, V. *Chem. Commun.* **2001**, 233–234. (c) Greedy, B.; Paris, J.-M.; Vidal, T.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2003**, *42*, 3291–3294. (d) Thibaudeau, S.; Gouverneur, V. *Org. Lett.* **2003**, *5*, 4891–4893. (e) Thibaudeau, S.; Fuller, R.; Gouverneur, V. *Org. Biomol. Chem.* **2004**, *2*, 1110–1112.

the synthesis of 2-fluoro-1,3-dienes from the corresponding allenylmethylsilanes (Scheme 1). This is the first route to

Scheme 1. Allenylmethylsilanes as Precursors of Fluorodienes



these valuable compounds that is not based on the use of a fluorinated building block. Indeed, fluorinated cyclopropanes⁷ and fluorinated unsaturated aldehydes⁸ are two of the most commonly used precursors of monofluorinated dienes, which are obtained upon ring opening and Wittig alkenylation, respectively. Other elegant routes toward fluorinated dienes have also been developed such as various elimination processes⁹ and palladium-mediated couplings of fluorinated precursors.¹⁰

To prepare the starting allenylmethylsilanes **1a–i**, we adapted a procedure described in the literature.^{4b,11} Several substituted trimethylsilylmethylbutadienes were obtained in good overall yields by the reaction of the propargylic mesylates **2a–i** freshly prepared from the corresponding alcohols **3a–i**, with $\text{Me}_3\text{SiCH}_2\text{MgCl}$ in the presence of an excess of CuCN and LiCl . The use of these two salts is essential for effecting γ -attack of the Grignard reagent leading to the exclusive formation of the desired allenylmethylsilanes. We found that the yields are consistently

superior if these reactions are carried out in THF at -78°C instead of in ether. The starting propargylic alcohols were prepared according to standard procedures from the literature (Table 1).¹²

Table 1. Preparation of Allenylmethylsilanes **1a–i**

entry	R	R'	product	yield (%)	product	yield (%)
1	PhCH_2CH_2	Me	2a	94	1a	81
2	BnOCH_2	Me	2b	95	1b	79
3	$n\text{C}_5\text{H}_{11}$	Ph	2c	74	1c	49
4	$n\text{C}_5\text{H}_{11}$	Me	2d	91	1d	83
5	PhCH_2CH_2	SiMe_3	2e	85	1e	69
6	PhCH_2CH_2	H	2f	99	1f	80
7	H	AcOCH_2	2g	87	1g	75
8	H	BnOCH_2	2h	64	1h	77
9	H	Ph	2i	71	1i	54

Our initial studies began with allenylsilane **1a** as the dienyl transfer reagent (Table 2). Reaction of **1a** with 1 equiv of

Table 2. Electrophilic Fluorination of Silane **1a**

entry	fluorinating reagent	solvent	additive	time (h)	yield 4a (%)
1	Selectfluor	acetonitrile		120	51 ^a
2	Selectfluor	acetone		120	49
3	Selectfluor	THF		120	5
4	Selectfluor	MeOH		21	43 ^b
5	Selectfluor	acetonitrile	NaHCO_3	27	60
6	Selectfluor	acetone	NaHCO_3	27	64
7	NFSI	acetone	NaHCO_3	48	39

^a **4a** was contaminated with 5% of **5a**. ^b Ratio of **4a**:**5a** = 2:1.

Selectfluor in acetonitrile afforded 51% of the desired fluorinated diene **4a** after 120 h. This compound was contaminated with 5% of the nonfluorinated diene **5a** resulting from a protodesilylation process (entry 1). The use of acetone as the reaction solvent did not result in any substantial changes, whereas THF was found not to be suitable for this transformation (entries 2 and 3). Methanol was also tested as a solvent for this transformation, allowing the formation of the desired diene **4a** along with the undesired nonfluorinated diene **5a** in 43% combined yield in a ratio of ca. 2:1 as judged by ^1H NMR analysis of the purified material after 21 h. As expected, this polar protic solvent favors the protodesilylation process but also sub-

(12) Experimental details can be found in Supporting Information.

(7) (a) Patrick, T. B.; Rogers, J.; Gorrell, K. *Org. Lett.* **2002**, *4*, 3155–3156. (b) Bessard, Y.; Kuhlmann, L.; Schlosser, M. *Tetrahedron* **1990**, *46*, 5230–5236. (c) Schlosser, M.; Dahan, R.; Cottens, S. *Helv. Chim. Acta* **1984**, *67*, 284–288. (d) Spahi, B.; Schlosser, M. *Helv. Chim. Acta* **1980**, *63*, 1242–1256. (e) Molines, H.; Wakselman, C. *Tetrahedron* **1976**, *32*, 2099–2103. (f) Seyferth, D.; Julia, T. F.; Mueller, D. C.; Mazerolles, P.; Manuel, G.; Thoumas, F. *J. Am. Chem. Soc.* **1970**, *92*, 657–666. (g) Weyerstahl, P.; Klamann, D.; Finger, C.; Fligge, M.; Nerdel, F.; Buddrus, J. *Chem. Ber.* **1968**, *101*, 3–1311. (h) Shi, G.-Q.; Schlosser, M. *Tetrahedron* **1993**, *49*, 1445–1456. (i) Shi, G.-Q.; Cottens, S.; Shiba, S. A.; Schlosser, M. *Tetrahedron* **1992**, *48*, 10569–10574.

(8) (a) Ni, J.; Liu, J.; Colmenares, L. U.; Liu, R. S. H. *Tetrahedron Lett.* **2001**, *42*, 1643–1644. (b) Liu, J.; Colmenares, L. U.; Liu, R. S. H. *Tetrahedron Lett.* **1997**, *38*, 8495–8498. (c) Francesca, A.; Alvarez, R.; López, S.; de Lera, A. R. *J. Org. Chem.* **1997**, *62*, 310–319. (d) Matsuo, N.; Kende, A. S. *J. Org. Chem.* **1988**, *53*, 2304–2308.

(9) Patel, S. T.; Percy, J. M.; Wilkes, R. D. *Tetrahedron* **1995**, *51*, 11327–11336. (b) Hedhli, A.; Bakloutti, A. *Tetrahedron Lett.* **1995**, *36*, 4433–4436.

(10) (a) Gernert, D. L.; Ajamie, R.; Ardecky, R. A.; Bell, M. G.; Leibowitz, M. D.; Mais, D. A.; Mapes, C. M.; Michellys, P. Y.; Rungta, D.; Reifel-Miller, A.; Tyhonas, J. S.; Yumibe, N.; Grese, T. A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3191–3195. (b) Peng, S.; Qing, F.-L.; Li, Y.-Q.; Hu, C.-M. *J. Org. Chem.* **2000**, *65*, 694–700.

(11) (a) Ajamian, A.; Gleason, J. L. *Org. Lett.* **2003**, *5*, 2409–2411. (b) Matsuda, F.; Kawatsura, M.; Hosaka, K.-I.; Shirahama, H. *Chem. Eur. J.* **1999**, *5*, 3252–3259. (c) Osa, Y.; Kobayashi, S.; Sato, Y.; Suzuki, Y.; Takino, K.; Takeuchi, T.; Miyata, Y.; Sakaguchi, M.; Takayanagi, H. *J. Med. Chem.* **2003**, *46*, 1948–1956. (d) Wipf, P.; Rahman, L. T.; Rector, S. R. *J. Org. Chem.* **1998**, *63*, 7132–7133. (e) Wrobel, J.; Li, Z.; Dietrich, A.; McCaleb, M.; Mihan, B.; Sredy, J.; Sullivan, D. *J. Med. Chem.* **1998**, *41*, 1084–1091.

stantially reduces the reaction time (entry 4). We suppressed fully the formation of the undesired nonfluorinated diene **5a** resulting from a protodesilylation process by adding 1.2 equiv of NaHCO₃ to the reaction mixture using acetonitrile or acetone as the reaction solvent (entries 5 and 6). The presence of the base not only prevents the formation of the non-fluorinated diene **5a**, therefore increasing the reaction yield, but also reduces substantially the reaction time (27 versus 120 h). The use of acetone facilitates the workup procedure and the purification of the product; therefore, this solvent was selected for subsequent reactions. Finally, we probe the reactivity of *N*-fluorosulfonimide¹³ under similar conditions, but the use of this alternative reagent as the electrophilic source of fluorine was not advantageous (entry 7).

The optimized reaction conditions were applied to various allenylsilanes **1b–i**, and the results are summarized in Table 3. The methodology allows the preparation of fluorodienes

Table 3. Fluorodesilylation of **1a–h** with Selectfluor^a

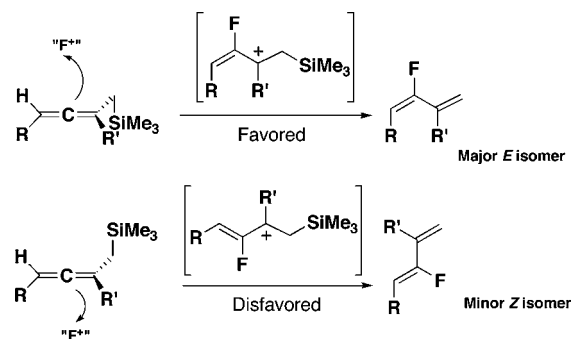
entry	allenylsilane	fluorodiene	yield (%) E/Z ratio
1			64 2/1
2			89 2/1
3			66 2/1
4			37 2/1
5			11 ^b 3/1
6			45 2/1
7			23 -
8			79 -
9			99 -

^a Conditions: 1 equiv of Selectfluor, 1.2 equiv of NaHCO₃, acetone, rt, up to 48 h. ^b Conversion assigned by ¹H NMR.

with different degrees of substitution. The dienes recovered after workup are sufficiently clean to be used without further purification. The yields range from 11 to 99% depending on the substitution pattern of the starting allenylsilane. The

best yields were obtained for substrates with a substituent that can reinforce the β -effect¹⁴ of the trimethylsilyl group upon addition of Selectfluor (entries 1–3, 8, and 9). As anticipated, the lowest yield of desired fluorinated diene was obtained for substrate **1e** as this allenylsilane features an additional trimethylsilyl group on a position where it destabilizes the development of positive charge upon addition of Selectfluor (entry 5). The presence of the electron-withdrawing acetyl group of the achiral substrate **1g** is probably responsible for the lower yield of the fluorinated diene **4g**. In contrast, the two additional achiral terminal allenylsilanes **1h,i** were transformed into the corresponding 2,3-disubstituted 1,3-dienes **4h** and **4i** in good yields (79 and 99%, respectively). The racemic allenylsilanes **1a–f** led to the formation of the desired di- or trisubstituted dienes as mixtures of *E/Z* isomers in a 2/1 ratio with the exception of diene **4e** that was formed as a 3/1 mixture of the *E/Z* isomers. The *E* isomer was the major product. These stereoisomers are difficult to separate upon purification. The *E/Z* ratio was determined by ¹H NMR, and the configuration of the double bond was assigned with the coupling constant of the vinyl proton and fluorine ((*E*)-**4** J_{H-F} = 22.0–28.0 Hz; (*Z*)-**4** J_{H-F} = 31.6–38.0 Hz). In this series, the nature of the substituent of the starting allenylsilane does not affect significantly the *E/Z* ratio of the fluorodienes.

Scheme 2. Suggested Mechanism and Preferential Formation of the *E* Isomer.



From a mechanistic point of view, we propose that Selectfluor reacts as an electrophile according to an S_E2' mechanism with the regiocontrolled addition of the fluorine leading to the development of the positive charge β to the trimethylsilyl group. The desilylation process restores neutrality and affords the desired fluorodiene. Our optimization studies revealed that the addition of NaHCO₃ prevents protodesilylation, thereby increasing the reaction yield. The formation of the major *E* isomer indicates that the electrophile approaches preferentially the central carbon of the allenylmethylsilane from the side opposite to the sterically demanding R substituent, with the organosilane adopting a reactive conformation, allowing early stabilization of the developing positive charge. This mechanistic pathway, well

(13) (a) Davis, F. A.; Han, W. *Tetrahedron Lett.* **1991**, 32, 1631–1634. (b) Davis, F. A.; Han, W. *Tetrahedron Lett.* **1992**, 33, 1153–1156. (c) Davis, F. A.; Han, W.; Murphy, C. K. *J. Org. Chem.* **1995**, 60, 4730–4737.

(14) Lambert, J. B.; Zhao, Y.; Emblidge, R. W.; Salvador, L. A.; Liu, X.; So, J.-H.; Chelius, E. C. *Acc. Chem. Res.* **1999**, 32, 183–190.

in line with what has been suggested for other electrophiles such as iminiums or aldehydes, contrasts with the reactivity of bridging electrophiles such as iodine and bromine. Indeed, these reagents are believed to add on the double bond remote from the silyl group to give a product of addition that is then treated in the presence of TBAF to trigger the elimination process leading to the formation of the corresponding 2-iodo- or 2-bromo-1,3-diene.⁵

In summary, we have shown that the concept of electrophilic fluorodesilylation can be applied to allenylmethylsilanes as an entry to 2-fluorodienes with various substitution patterns. The methodology is best applied to fluorodienes that cannot be formed as mixtures of *E/Z* isomers. This is the first route to these compounds not based on the use of fluorinated building blocks. We are currently expanding this chemistry to more elaborated fluorinated dienes using

bifunctional allenylmethylsilanes that allow the sequential addition of two electrophiles, one of them being Selectfluor.

Acknowledgment. We thank Marc Gingell and Dr. Sarah Lee for preliminary synthetic efforts on this project. This work was generously supported by the Spanish Ministry of Education (EX-31/10/03) and the European Community (MEIF-CT-2004-515589) through funding to MP.

Supporting Information Available: Experimental details and spectroscopic data for all new propargylic alcohols, mesylates, allenylmethylsilanes, and fluorodienes. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL047319Z