

Fluorodesilylation of alkenyltrimethylsilanes: a new route to fluoroalkenes and difluoromethyl-substituted amides, alcohols or ethers

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A range of alkenyltrimethylsilanes are converted to alkenyl fluorides by reaction with one equivalent of Selectfluor™ (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)), or difluoromethyl-substituted alcohols, ethers or amides using an excess of Selectfluor™ in the presence of various nucleophiles.

In view of the unique features of fluorine-containing compounds, there has been an increasing interest in the development of novel methods for the synthesis of fluorinated molecules.¹ In particular, terminal fluoroalkenes have been used in the design of a number of mechanism-based enzyme inhibitors and other bioactive molecules.² Consequently, development of general methodologies for their preparation is an important challenge. Our studies were initiated in order to investigate the hypothesis that electrophilic N–F reagents³ would react with alkenyltrimethylsilanes to give the corresponding alkenyl fluorides. Fluorodesilylations of aryltrimethylsilanes using xenon difluoride and elemental fluorine have been reported respectively by Lothian and Ramsden⁴ and by Stuart *et al.*⁵ Surprisingly, in contrast to chloro-, bromo- or iododesilylation,⁶ fluorodesilylation has never been applied to alkenylsilanes. In addition, the reactivity of the N–F group of reagents has not been investigated for a fluorodesilylation processes. In this communication, we demonstrate a new and facile approach for the synthesis of alkenyl fluorides as well as difluoromethyl-substituted alcohols, amides and ethers.

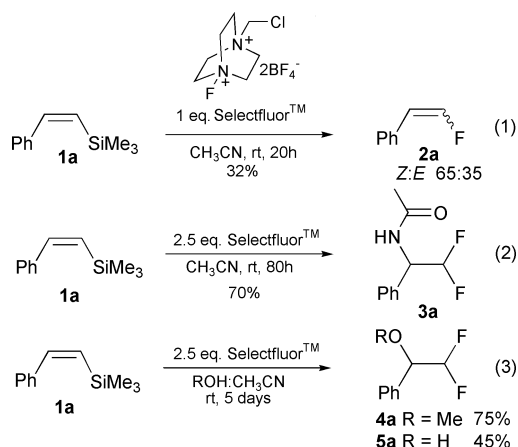
The substrate trimethylstyrylsilane **1a** was prepared as a mixture of stereoisomers (*E*:*Z*/8:92).⁷ The fluorodesilylation was attempted with several commercially available N–F reagents. The reaction of compound **1a** with 1 eq. of Selectfluor™ in acetonitrile at rt afforded the expected fluoroalkene **2a** with a conversion⁸ of 47% after 20 h (Scheme 1, eqn 1 and Table 1, entry 1). Prolonged reaction times did not improve the yield of compound **2a** as the formation of a second product was observed instead. This product was identified as difluoroamide **3a** and is believed to result from further fluorination of **2a** followed by reaction with acetonitrile. When

1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(trifluoromethanesulfonate) was allowed to react with an equimolar amount of compound **1a** in acetonitrile, fluorodesilylation occurred to afford the fluoroalkene **2a** with a conversion of 32%. In contrast, 1-fluoropyridinium pyridine heptafluorodiborate and *N*-fluorobenzenesulfonimide did not react with compound **1a**. These results prompted us to use Selectfluor™ for subsequent fluorodesilylation reactions. A series of alkenyltrimethylsilanes **1b–f** was thus prepared according to known literature procedures^{7,9} in order to evaluate the scope and limitation of this reaction. The expected fluoroalkenes **2b,c** were obtained as *Z*:*E* mixtures in moderate to good yields (Table 1, entries 2 and 3). In terms of mechanism, the reaction of **1a** to form **2a** might involve an

Table 1 Fluorodesilylation of vinylsilane derivatives **1a–f**

Entry	Substrate	Product	Yield (%) ^a (Conversion (%) ^b)
1			32 (47) <i>Z</i> : <i>E</i> 65:35
2			(45) <i>Z</i> : <i>E</i> 80:20
3			57 (65) <i>Z</i> : <i>E</i> 58:42
4			70 (74)
5			0
6			86 (88)
7			55 (70)
8			75 (82)
9			45 (46)
10			79 (87)
11			83 (90)
12			6e <i>n</i> = 1 62 6f <i>n</i> = 2 48

^a Chemical yield after column chromatography. ^b Evaluated by GCMS.



Scheme 1

addition–elimination pathway *via* a carbocationic intermediate. The formation of a mixture of geometrical isomers and the faster reaction with more nucleophilic vinylsilanes are consistent with this mechanism.

Treatment of alkenylsilanes **1a–d** with more than one equivalent of SelectfluorTM produced the corresponding vicinal difluoroamides **3a**, **3c** and **3d** in good yields by a Ritter-type fluoro-functionalisation with acetonitrile (Scheme 1, eqn. 2 and Table 1, entries 4, 6 and 7). The reaction could not be applied to **1b** since the corresponding primary product of the reaction, the fluoroalkene **2b**, failed to react any further (Table 1, entry 5). These results are consistent with the observation made earlier by Stavber *et al.*¹⁰ who reported that monofluoroamides could be prepared from the corresponding alkene by a “fluoro-Ritter” reaction. More recently, Olah *et al.*¹¹ also reported the formation of difluoroamides by electrophilic fluorination of alkenyl boronic acids and trifluoroborates.

When the reaction was carried out in aqueous acetonitrile or in a mixture of methanol and acetonitrile, the product outcome was different (Scheme 1, eqn. 3). When the alkenyltrimethylsilanes **1a** and **1c** were treated with 2.5 eq. of SelectfluorTM in a 1:1 mixture of MeOH–CH₃CN, the corresponding difluoro-methyl ether derivatives **4a** and **4c** were prepared in 75 and 79% yield respectively (Table 1, entries 8 and 10). Similarly, when compounds **1a** and **1c** were treated with 2.5 eq. of SelectfluorTM in a 1:1 mixture of H₂O:CH₃CN, the difluoromethyl alcohols **5a** and **5c** were obtained with chemical yields of 45 and 83% (Table 1, entries 9 and 11). The difluoroamides were always formed as side products but could be easily separated by silica gel chromatography. In addition, the methodology can also be applied to the preparation of the bis-fluorinated tetrahydrofuran **6e** and the tetrahydropyran **6f**[†] by treating the corresponding alkenyltrimethylsilanes **1e** and **1f** with 2.5 eq. of SelectfluorTM in acetonitrile (Table 1, entry 12).

In summary, substituted alkenylsilanes carrying electron-donating groups undergo smooth mono- or bis-electrophilic fluorination to afford fluoroalkenes or vicinal difluoroamides, alcohols or ethers. The present report opens new possibilities for the direct and effective preparation of alicyclic and cyclic difluorinated derivatives. Mechanistic investigations along with the evaluation of the scope and limitation of this novel methodology are in progress in our laboratory. The generous financial support of Rhodia Organique Fine is acknowledged. We also thank Dr J. M. Paris, Dr J. R. Desmurs, and Dr J. Russell for very helpful suggestions regarding this work.

Notes and references

[†] Procedure for the production of **6f**: A solution of 5-phenyl-6-trimethylsilyl hex-5-en-1-ol (350 mg, 1.4 mmol) in acetonitrile (35 ml) was treated with SelectfluorTM (1.24 g, 3.5 mmol) and stirred at rt for 48 h. The reaction mixture was poured into saturated aqueous sodium hydrogen carbonate (30 ml) and extracted with diethyl ether (3 × 30 ml). The combined organic phases were dried (MgSO₄) and concentrated *in vacuo*. Purification of the residue by silica gel chromatography (1:1 hexane–DCM, *R*_f = 0.48) gave the product as a colourless oil (142 mg, 48%); ¹H NMR (400 MHz, CDCl₃): 1.42–1.52 (m, 2H), 1.69–1.79 (m, 2H), 1.96 (td, 1H, *J* = 13.6, *J* = 4Hz), 3.53 (td, 1H, *J* = 12.4Hz, 2.4), 3.80–3.84 (m, 1H), 5.57 (t, 1H, *J* = 57.2 Hz), 7.35–7.50 (m, 5H); ¹³C NMR (100.6 MHz, CDCl₃): 18.4, 25.3(t, *J* = 2.3Hz), 25.6, 29.7, 62.5, 117.1 (t, *J* = 247.8 Hz), 128.1, 128.3, 128.6 and 135.4; ¹⁹F NMR (235.3 MHz, CDCl₃): –131.1, –131.9 (dxAB, *J*_{F–F} = 277.6 Hz, *J*_{H–F} = 56.5 Hz); HRMS calcd. for C₁₂H₁₈NOF (M + NH₄)⁺ 230.1356, found 230.1349.

- (a) *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*, ed. R. Filler, Y. Kobayashi and L. M. Yagupolskii, Elsevier, Amsterdam, 1993; (b) *Fluorine-Containing Amino Acids: Synthesis and Properties*, ed. V. P. Kukhar and V. A. Soloshonok, John Wiley & Sons, Chichester, 1995.
- (a) *Biomedical Frontiers of Fluorine Chemistry*, ed. I. Ojima, J. R. McCarthy and J. T. Welch, American Chemical Society, Washington DC, 1996; (b) *Synthetic Fluorine Chemistry*, ed. G. A. Olah, R. D. Chambers and G. K. S. Prakash, John Wiley & Sons, New York, 1992; (c) *Organofluorine Chemistry: Principles and Commercial Applications*, ed. R. E. Banks, B. E. Smart and J. C. Tatlow, Plenum Press, New York, 1994; (d) *Effects of Selective Fluorination on Reactivity*, P. Bey, J. R. McCarthy and I. A. McDonald, ACS Symposium Series 456, American Chemical Society, Washington DC, 1991, 105.
- G. S. Lal, G. P. Pez and R. G. Syvret, *Chem. Rev.*, 1996, **96**, 1737 and references therein.
- A. P. Lothian and C. A. Ramsden, *Synlett*, 1993, **10**, 753.
- A. Stuart, P. L. Coe and D. J. Moody, *J. Fluorine Chem.*, 1998, **92**, 179.
- The Chemistry of Organic Silicon Compounds Part 2*, ed. S. Patai and Z. Rapoport, John Wiley & Sons, Chichester, 1989.
- R. B. Miller and G. J. McGarvey, *J. Org. Chem.*, 1978, **23**, 4424.
- The term ‘conversion’ is used here to mean the total % of product detected in the reaction mixture by GCMS before isolation.
- (a) N. Chatani, N. Amishiro, T. Morii, T. Yamashita and S. Murai, *J. Org. Chem.*, 1995, **60**, 1834; (b) C. Flann, T. C. Malone and L. E. Overman, *J. Am. Chem. Soc.*, 1987, **109**, 6097.
- S. Stavber, T. S. Pecan, M. Papez and M. Zupan, *Chem. Commun.*, 1996, **19**, 2247.
- N. A. Petasis, A. K. Yudin, I. A. Zavialov, G. K. S. Prakash and G. A. Olah, *Synlett*, 1997, **5**, 606.