Synthesis of Difluoroenoxysilanes from Acylsilanes and Trifluoromethyltrimethylsilane (TFMTMS). Dramatic Effect of the Catalytic Fluoride Source

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Difluoroenoxysilanes are produced in high yield by catalytic fluoride activation of a mixture of TFMTMS and an acylsilane: Tetrabutylammonium difluorotriphenylstannate is an excellent catalyst whereas tetrabutylammonium fluoride leads directly to the aldol product corresponding to the difluoromethyl ketone. Some one-pot applications illustrate the usefulness of this methodology.

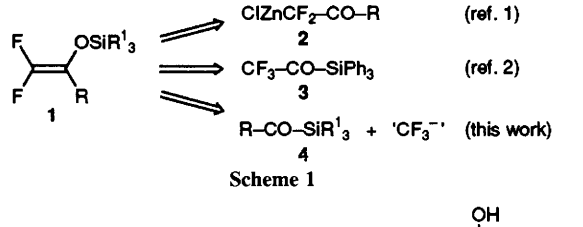
Difluoroenoxysilanes **1** (Scheme 1) are useful difluoroenolate equivalents first prepared by silylation of zinc difluoroenolates **2**,[1] and more recently by the addition of an organometallic reagent to trifluoroacetyltriphenylsilane **3**,[2] in the latter method, all applications reported involved trifluoroacetyltriphenylsilane **3** (R^1 = Ph).[3]

While studying the properties of acylsilanes,[4] we have used the Brook rearrangement to develop new organofluorosilicon intermediates.[5–9] Having prepared higher perfluoroenoxysilane analogues by a one-pot sequence,[7] we studied the synthesis of difluoroenoxysilane **1** by a similar strategy, more versatile than that from **3** allowing variation of both acyl and silyl part of **4**. As the trifluoromethyl anion source we chose trifluoromethyltrimethylsilane[10] (TFMTMS) under fluoride activation.[11]

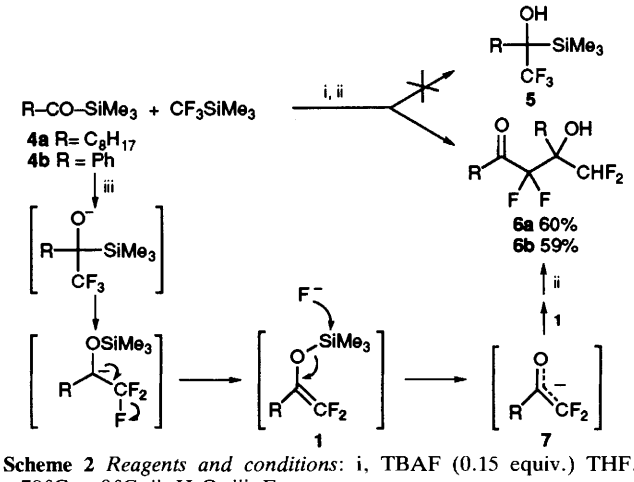
A mixture of **4a** and TFMTMS (1.2 equiv.) was treated with 0.15 molar equivalent of tetrabutylammonium fluoride (TBAF) in THF at low temperature (−78 °C) in order to attempt to isolate the alcohol **5** (Scheme 2). Neither **5** nor the expected **1a** was detected, but the reaction gave cleanly, even at 0 °C, a product with spectral features consistent with the structure **6**,† which derived formally from aldol condensation of the corresponding difluoromethyl ketone, in 60% yield. A difluoroenolate is probably generated *in situ* and the path depicted in Scheme 2 is a tentative explanation of the formation of **6**. The enoxysilane **1**, formed after the Brook rearrangement, would be immediately converted into enolate **7** under fluoride attack (*vide infra*). Thus **1** would act as a nucleophile (difluoroenolate equivalent) as well as an electrophilic substrate leading to **6**. This dual behaviour has already been observed by us for higher homologues[7] and by Nakai *et al.* for perfluoroenolate.[12]

To avoid this self condensation, we needed to inhibit the nucleophilic activation of **1** by the fluoride anion by using a less nucleophilic source of fluoride. Tetrabutylammonium difluorotriphenylstannate (DFTPS) ($Bu_4N^+Ph_3SnF_2^-$) has recently been reported to be less nucleophilic than TBAF,[13] so we prepared and used this salt and were gratified to obtain the expected difluoroenoxysilane very cleanly and conveniently (0.01 equiv. of DFTPS, 0 °C, 1 h) (Scheme 3 and Table 1). Starting from the acyltrimethylsilanes **4a,b** the enoxysilanes **1a,b** were formed in high yields (entries 1 and 2) but were too easily hydrolysed during work-up and purification to be isolated as pure materials. However, the *tert*-butyldimethylsilyl analogues **1c,d** were isolated in high yield (entries 3 and 4). This reaction can be carried out in THF, diethyl ether and even dichloromethane with an equal efficiency. So one-pot reactions under nucleophilic or Lewis acid activation can be expected. To assess the mechanism claimed in Scheme 2, a catalytic amount of TBAF (0.2 equiv.) was added to the difluoroenoxysilane **1b** generated *in situ* from **4b** and TFMTMS in diethyl ether. The condensation compound **6b** was indeed the major product confirming the crucial importance of the fluoride source.

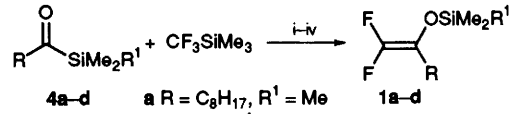
The one-pot reactions shown in Scheme 4 and 5 illustrate the potential of this methology, although they would need further optimization. Dilute acidic hydrolysis converted **1a** quantitatively (GC, NMR) into the corresponding difluoromethylketone **8**. The *tert*-butyldimethylsilyl derivative **1c**



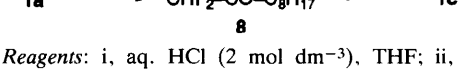
Scheme 1



Scheme 2 *Reagents and conditions*: i, TBAF (0.15 equiv.) THF, −78 °C or 0 °C; ii, H_2O; iii, F^-.



Scheme 3 *Reagents and conditions*: i–iv, $Bu_4N^+Ph_3SnF_2^-$(cat), solvent as entries 1–4, Table 1.

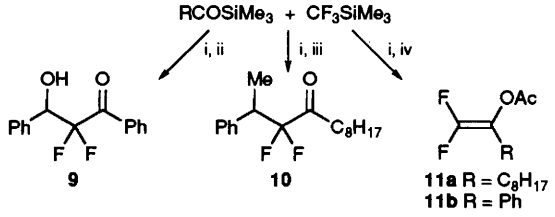


Scheme 4 *Reagents*: i, aq. HCl (2 mol dm^{-3}), THF; ii, TBAF, THF–H_2O.

Table 1 Synthesis of difluoroenoxysilanes

Entry	Acylsilane	DFTPS (equiv.)	Conditions solvent, temp./°C, time/h	Product[a]
1	**4a**	0.01	THF, −78 to −20, 4	**1a** 44 (quant.)
2	**4b**	0.01	CH_2Cl_2, 0, 1	**1b** (quant.)
3	**4c**	0.25	THF, −78 to −20, 1	**1c** 75
4	**4d**	0.25	THF, −78 to −20, 1	**1d** 79

[a] Isolated yield. GC or NMR estimated yield in parenthesis.



Scheme 5 *Reagents and conditions*: i, DFTPS (0.01 equiv.), CH_2Cl_2, 0 °C, 30 min.; ii, $TiCl_4$ (1.5 equiv.), PhCHO (1.2 equiv.), −78 °C, then room temp., 20 h, 71%; iii, $ZnBr_2$ (1.2 equiv.) PhCH(Me)Br, 12 h, 50%; iv, $ZnBr_2$ (1.2 equiv.), MeCOCl, 12 h, **11a**: 60%, **11b**: 61%.

needed a treatment by TBAF in wet THF to give **8**. The fair isolated yield of **8** (57%) was due to their partial hydration and the small scale of the experiment. The Mukayiama aldol reaction was performed by adding $TiCl_4$ and benzaldehyde to the crude solution of **1b** cooled at −78 °C. After 20 hours stirring at room temperature, the corresponding aldol **9**,‡ was isolated in 71% overall yield. Addition of $ZnBr_2$ and 1-bromo-1-phenylethane to **1a** prepared in CH_2Cl_2 gave the corresponding benzylated difluoro derivative **10**,§ in 50% overall isolated yield. Addition of $ZnBr_2$ and acetyl chloride to the crude solution of **1a** or **1b** in CH_2Cl_2 gave exclusively the O-acylated corresponding product **11a** and **b** as it has already been observed.[1]

In summary, the anionic trifluoromethylation of acylsilanes using TFMTMS is a new, efficient and versatile method to synthesize difluoroenoxysilanes which can be used *in situ* to prepare various difluoromethylene compounds. This study emphasizes the importance of the choice of the activating fluoride and reveals the electrophilic character of the difluoroenoxysilane.

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Footnotes

† **6a**: ^{1}H NMR ($CDCl_3$; 250 MHz; *J*/Hz) δ 1.84 (t, $^3J_{HH}$ 8, CH_2COH), 2.76 (td, J_{HH} 7, $^4J_{HF}$ 1.3, CH_2CO), 3.64 (s, OH), 5.89 (td, $^2J_{HF}$ 55, $^4J_{HF}$ 1.2, CHF_2); ^{13}C NMR ($CDCl_3$; 62.89 MHz, *J*/Hz) δ 76.7 (m, COH), 114.8 (t, $^1J_{CF}$ 250, CHF_2), 113.5 (t, $^1J_{CF}$ 264, CF_2), 202.9 (t, $^2J_{CF}$ 29, CO); ^{19}F NMR ($CDCl_3$, 235.36 MHz; *J*/Hz) δ/$CFCl_3$ − 115.6 (d, $^2J_{FF}$ 282, 1F, CF_2), −117.6 (d, $^2J_{FF}$ 282, 1F, CF_2), −129.8 (dd, $^2J_{FF}$ 290, $^2J_{HF}$ 54, CHF), −131.4 (dd, $^2J_{FF}$ 290, $^2J_{HF}$ 54, CHF); *m*/*z* (70 ev) 159 (M^+ −225, 1), 141 (100), 71 (22), 57 (33), 55 (17). Found: C, 62.50; H, 9.82. Calc: C, 62.48; H, 9.44%).

‡ **9**: ^{1}H NMR ($CDCl_3$; 250 MHz; J/Hz) δ 3.10 (d, $^3J_{HH}$ 4.6, OH), 5.27 (dt, $^3J_{HF}$ 18.6, $^3J_{HH}$ = $3J_{HF}$, 4.6, CH); ^{13}C NMR ($CDCl_3$; 62.89 MHz; J/Hz) δ 73.4 (dd, $^2J_{CF}$ 27.6, $^2J_{CF}$ 21.7, CH) 118 (dd, $^1J_{CF}$ 263.8, $^1J_{CF}$ 258, CF_2), 191 (t, $^2J_{CF}$ 29.3, CO); ^{19}F NMR ($CDCl_3$, 235.36 MHz J/Hz) δ/$CFCl_3$ − 108. 1 (dd, $^2J_{FF}$ 292, $^3J_{HF}$ 4.6, CF_2), −116.8 (dd, $^2J_{FF}$ 292, $^2J_{HF}$ 18.6, CF_2).

§ **10**: ^{1}H NMR ($CDCl_3$; 250 MHz; *J*/Hz) δ 1.44 (d, $^3J_{HH}$ 7, CH_3CH), 2.14 (dtm, J_{AB} 18.6, $^3J_{HH}$ 6.5, CH_2CO), 2.42 (dtm, J_{AB} 18.6, $^3J_{HH}$ 6.5, CH_2CO), 3.49 (m, CH), 7.08–7.36 (m, Ar); ^{13}C NMR ($CDCl_3$; 62.89 MHz; *J*/Hz) δ 13.6 (CH_3CH), 14.1 (CH_3), 22.3, 22.6, 28.7, 29.0, 29.1, 31.7, 37.8 (CH_2), 43.0 (t, $^2J_{CF}$ 22.5, CH), 127.8–129.0 (Ar), 202.5 (t, $^2J_{CF}$ 30, CO); ^{19}F NMR ($CDCl_3$, 235.36 MHz; *J*/Hz) δ/$CFCl_3$ − 109.2 (dd, *J* 259, $^3J_{FH}$ 13, 1F, CF_2), −117.4 (dd, *J* 259, $^3J_{FH}$ 20, 1F, CF_2), *m*/*z* (70 ev) 296 (M^+, 17), 141 (100), 105 (21), 71 (88), 57 (74). (Found: C, 73.09; H, 9.11. Calc: C, 72.94; H, 8.84%).

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