Pergamon

Tetrahedron Letters 39 (1998) 3137–3140

TETRAHEDRON LETTERS

Electrosynthesis of New Functionalized Difluoro Allylsilanes.

Michael Rajaonah,[#§] Michael H. Rock,[#] Jean-Pierre Bégué,*[#] Danièle Bonnet-Delpon,[#] Sylvie Condon,[§] Jean-Yves Nédélec,[§]

[1#]Laboratoire BIOCIS associé au CNRS, Centre d'Etudes Pharmaceutiques, Châtenay-Malabry, 92296 Cedex France.
[§]LECSO CNRS-Université Paris 12, 2, rue Henry Dunant, BP 28, 94320 Thiais;

Received 29 January 1998; accepted 25 February 1998

Abstract: An efficient electrochemical silylation of chlorodifluoromethyl enol ethers **2** afforded in good yields the new functionalized difluoromethyl allylsilanes **1** on a preparative scale. These silanes reacted as difluoromethyl anion equivalents with an aldehyde as electrophile, providing functionalized α-difluoromethyl alcohols **4**.

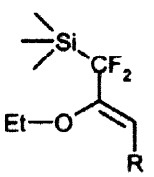
Trifluoromethyltrimethylsilane (Ruppert's reagent) was a great progress to direct nucleophilic trifluoromethylation methods.[1] It has been widely used to introduce a CF_3 group in a wide variety of carbonyl compounds,[2,3] and in sulfenyl and sulfonyl derivatives,[4] and for cross-coupling reactions with halides.[5] Easy handling in mild conditions, possible enantioselective addition,[6,3] as well as its recently improved preparation using an aluminum anode,[7] or aluminum powder,[8] make this agent a valuable synthetic tool.

This method has been extended to higher perfluoroalkylsilanes[3] and more recently, preparation and reactivity of difluoroalkyl silanes have been described.[3,9,10] Considering the great interest in introducing a CF_2 moiety into biomolecules, we focused our efforts to the preparation of difluoroallylsilanes where the CF_2 group is already substituted by a functionalized chain. The development of an efficient synthesis of silanes **1** from the corresponding chlorodifluoromethyl-substituted enol ethers **2** could present several advantages: enol ethers are easily prepared from the cheap precursor chlorodifluoro acetic acid,[11] and the organosilicon reagents **1** could react by two major pathways: as a difluoromethyl anion equivalent[12] or as an allyl silane.[13]

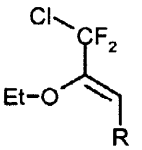
[1] Fax 33 1 46 83 57 40; e-mail Jean-Pierre.Begue@cep.u-psud.fr

0040-4039/98/$19.00
PII: S0040-4039(98)00462-6

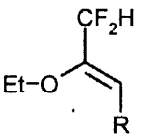
A difficulty could arise from the fact that the activation of C-Cl bond in a CF_2Cl group is not so easy. Only few examples of formation of C-C or C-Metal bond have been reported. The preparation of a silane from $ClCF_2H$ is described with only 35% yield.[14] Most of the reported examples concern radical cyclisations,[15] or reactions with compounds where C-Cl bond is weakened by an activating neighbouring group, such as difluorophenacyl chloride, chlorodifluoromethylsilanes,[10] and chlorodifluoroesters. The Reformatsky-type reaction with these latter are less effective than with corresponding bromides and iodides, in particular for condensation with aliphatic aldehydes, which often failed.[17]



1



2



3

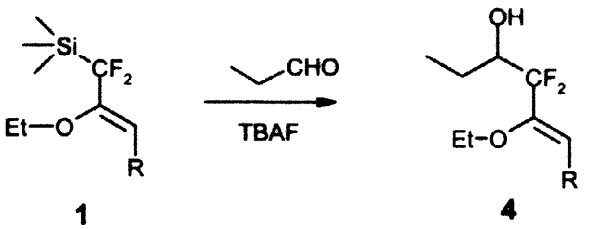
a = C_6H_5
b = CH_2-CH_2-C_6H_5

From enol ethers **2**, we effectively noticed that, unlike in corresponding epoxyethers,[18] the C-Cl bond is strong enough to be unreactive towards butyllithium. Considering the efficient two step reductive cleavage of $ArCF_2Cl$ by SmI_2,[16] and the easy electroreductive cross-coupling between CF_3Br and Me_3SiCl, we envisaged an electrochemical silylation of chlorodifluoromethyl enol ethers **2** for the synthesis of the new functionalized CF_2 allylsilanes **1**. Although the cathodic reduction of **2a** occurs at -1.9 V /SCE (Standard Calomel Electrode), this value is still 0.7 V positive to the reduction potential of Me_3SiCl. We thus used the precedently described conditions of electrosynthesis.[19] with a soluble anode process which can allow the reaction to occur in an individed cell, according to the following mechanism:

anodic reaction	$Mg - 2e \longrightarrow Mg^{2+}$	
cathodic reaction	$RCF_2Cl + 2e \longrightarrow RCF_2^- + Cl^-$	
nucleophilic displacement	$RCF_2^- + Me_3SiCl \longrightarrow RCF_2SiMe_3 + Cl^-$	

In preliminary experiments, 3 mmol of enol ether **2a** reacted in dimethyl formamide (DMF) with 2 equiv. of freshly distilled Me_3SiCl, in the presence of NBu_4Br, under a constant current of 0.06 A, with two different anodes, Al and Mg. The electrolysis was conveniently monitored by GC. Conversion was low (20%) with Al anode and complete with the Mg one. However, the allylsilane was accompanied with traces of reduced compound **3a** (5%) and an unidentified compound (35%), probably resulting of a reaction with DMF (according to MS spectrum). The amount of this compound could be deeply reduced when the reaction

was performed with 4 equiv. of Me_3SiCl. Finally the large-scale reaction with the enol ether **2a** (17 mmol) provided in 5 h the silane **1a** in an excellent isolated yield (94%)..[20] In same conditions, the allylsilane **1b** could also been obtained but after a longer reaction time (23 h) and in a lower yield (66%).



1 **4**

To check the potentialities of silanes **1** as CF_2-anion equivalents, we reacted in preliminary experiments, the silane **1a** with propanal in the presence of TBAF, 3 H_2O. Although the reaction was very slow (4 days), the condensation with the aldehyde occurred at 0 °C, leading to the alcohol **4a** in a 51% yield.[21] Under the same conditions **1b** led to the alcohol **4b** in a 49 % yield. Despite of these non optimized conditions, this promising reactivity is of great interest for the preparation of peptide isosteres, such as difluoromethylene dihydroxyamino propane unit, since we have shown that fluoroalkyl enol ethers can be stereoselectively converted into *syn* or *anti* amino alcohols.[22]

The electrochemical procedure described here is particularly convenient for the synthesis of the functionalized difluoroallyl silanes **1** on a preparative scale, starting from the easily accessible enol ethers **2** and despite of the low lability of a chlorine atom in a CF_2Cl moiety. Acting as CF_2-anion equivalents, these new silanes present the great advantage to introduce the CF_2 moiety into molecules along with an enol ether functionality which offers a wide range of reactivity. The development of related reactions and complete study of reactivity of allylsilanes **1** are under investigation.

References and notes

(1) Ruppert, I.; Schlich, K.; Volbach, W. *Tetrahedron Lett.* **1984**, *25*, 2195-2198.
(2) Krishnarmurti, R.; Bellew, D.R.; Prakash, G.K.S *J. Org. Chem.* **1991**, *56*, 984-989. Stahly G.P.; Bell D. R. *J. Org. Chem.* **1989**, *54*, 2873-2877.
(3) Prakash, G.H., Yudin, A.K. *Chem. Rev.* **1997**, *97*, 757-786, and references therein.
(4) Movchun, V.N.; Kolomeitsev, A.A.; Yagupolskii, Y. L. *J. Fluorine Chem.* **1995**, *70*, 255-**xx**. Billard, T.; Langlois, B. *Tetrahedron Lett.* **1996**, *37*, 6865-**xx**.
(5) Urata, H.; Fuchikami, T. *Tetrahedron Lett.*, **1991**, *32*, 91-94.
(6) Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron Lett.* **1994**, *35*, 3137-3158. Iseki, K.; Kobayashi, Y. *Rev. Heteroat. Chem.* **1995**, *12*, 211-237.
(7) F. Aymard, F.; Nédélec, J.Y.; Périchon, J. *Tetrahedron Lett.* **1994**, *35*, 8623-8624. Prakash, G.K.S.; Deffieux, D.; Yudin, A.K.; Olah, G.A. *Synlett* **1994**, 1057-1058.
(8) Grobe, J.; Hegge, J. *Synlett*, **1995**, 641-642.
(9) Hagiwara, H.; Fuchikami, T. *Synlett*, **1995**, 717-718.
(10) Yudin, A. K.; Prakash, G. K. S.; Deffieux, D.; Bradley, M.; Bau, R.; Olah, G. A. *J. Am. Chem. Soc.* **1997**, *119*, 1572-1581.
(11) Bégué, J.P.; Mesureur, D. *J. Fluorine Chem.* **1988**, *39*, 271-282. Bégué, J.P.; Bonnet-Delpon, D.; Née,

G.; Wu, S.W. *J. Org. Chem.* **1992**, *57*, 3807-3814. Bégué, J.P.; Bonnet-Delpon, D.; Kornilov, A. *Organic Syntheses, Vol. 75*, in press.

(12) Fujita, M.; Obayashi, M.; Hiyama, T. *Tetrahedron* **1988**, *44*, 4135-4145.

(13) Fleming, I. "Comprehensive Organic Chemistry"; Vol. 3, Barton, D., Ollis, W. D., Eds.; Pergamon Press: Oxford, 1979; p 541. Sakurai, H. *Pure Appl. Chem.* **1982**, *54*, 1.

(14) Fuchikami, T.; Ojima, I. *Journal of Organomet. Chem.* **1981**, *212*, 145-153.

(15) Arnone, A.; Bravo, P.; Viani, F.; Cavicchio, G. *Tetrahedron Asymmetry* **1991**, *2*, 399-402. Barth, F.; O-Yang, C.*Tetrahedron Lett.* **1991**, *32*, 5873-5876.

(16) Yoshida, M.; Suzuki, D.; Iyoda, M. *J. Chem. Soc. Perkin Trans. 1*, **1997**, 643-648.

(17) Lang, R.W.; Schaub, B.*Tetrahedron Lett.* **1988**, *29*, 2943-2946. Hu, Q.-S.; Hu, C.-M. *J. Fluor. Chem.* **1997**, *83*, 87-88. Tsukamoto, T.; Kitazume, T. *Synlett* **1992**, 977-979.

(18) Bégué, J.P.; Bonnet-Delpon, D.; Rock, M.H. *Tetrahedron Lett.* **1994**, *35*, 6097-6100.

(19) Chaussard, J.; Folest, J. C.; Nédélec, J. Y.; Sibille, S.; Périchon, J.; Troupel, M. *Synthesis* **1990**, 369-381 and references herein.

(20) **Typical procedure:** The reaction was conducted in a cylindral undivided cell, fitted with a magnesium rod as anode and a nickel foam cathode under Ar. Enol ether **2a** (4.36 g, 17 mmol) and freshly distilled TMSCl (8.7 mL, 4 mol equiv.) were added to a solution of DMF (50 mL) containing NBu_4Br (100 mg). The electrolysis was performed under a constant current (i = 0.06 A) until total conversion of starting material. After extraction with Et_2O, organic phases were washed (HCl 1 N and then brine) and dried ($MgSO_4$). Solvents were evaporated and residue gave after filtration on SiO_2 column (pentane/ether: 95/5), pure silane **1a** (4.36 g, 94 %) as a colorless liquid.

1a: ^{19}F NMR δ -116.0 (s, CF_2); ^1H NMR δ 0.05 (s, 3 H, CH_3-Si), 0.15 (s, 6 H, CH_3-Si), 1.18 (t, J = 7 Hz, 3 H, CH_3-CH_2), 3.77 (q, J = 7 Hz, CH_2-CH_3), 6.11 (s, 1 H, CH=C), 7.3 (m, 5 H, C_6H_5); ^{13}C NMR δ -4.2, 1.8, 15.3, 67.8, 113.7 (t, $^3J_{CF}$ = 8 Hz, CH=CCF_2-), 125.5 (t, $^1J_{CF}$ = 266 Hz, CF_2), 128.2, 128.8, 129.3, 130.8, 134.3, 151.7 (t, $^2J_{CF}$ = 19 Hz, C-CF_2Si). Anal. Calcd. for $C_{14}H_{20}F_2OSi$: C, 62.18; H, 7.47. Tr C, 62.12; H, 7.55.

1b: ^{19}F NMR δ -115.5 (s, CF_2); ^1H NMR δ 0.23 (s, 9 H, CH_3-Si), 1.32 (t, J = 7 Hz, 3 H, CH_3-CH_2), 2.57 (m, 2 H, C=C-CH_2), 2.78 (t, J = 7 Hz, CH_2-C_6H_5), 3.86 (q, J = 7 Hz, CH_2-CH_3), 5.45 (s, 1 H, CH=C), 7.35 (m, 5 H, C_6H_5); ^{13}C NMR δ -4.1, 1.2, 15.7, 26.9, 35.8, 69.2, 115.8 (t, $^3J_{CF}$ = 8 Hz, CH=CCF_2), 125.8 (t, $^1J_{CF}$ =264Hz CF_2), 126.1, 128.5, 128.6, 131.1, 141.7, 151.4 (t, $^2J_{CF}$ = 20 Hz, C-CF_2Si). Anal. Calcd. for $C_{16}H_{24}F_2OSi$: C, 64.38; H, 8.12. Tr C, 64.22; H, 8.28.

(21) A solution of propanal (64 mg, 1 mmol) in THF (6 mL) was treated at 0 °C with silane **1a** (300 mg, 1.1 mmol) in the presence of TBAF, $3H_2O$ (20 mg). Reaction mixture was stirred for 4 days, a HCl 1M solution was added and after extraction with diethyl ether, organic phases were dried ($MgSO_4$) and concentrated. Chromatography on SiO_2 provided alcohol **4a** (0.145 g, 51 %). **4a** ^{19}F NMR δ -112.7 (dd, $^2J_{FF}$ = 250 Hz, $^3J_{FH}$ = 20 Hz, 1F), -114.5 (dd, $^2J_{FF}$ = 250 Hz, $^3J_{FH}$ = 25 Hz, 1F); ^1H NMR δ 0.9 (t, J = 7 Hz, 3 H, CH_3-CH_2), 1.2 (m, 2 H), 1.22 (t, J = 7 Hz, 3 H, CH_3-CH_2), 3.80 (q, J = 7 Hz, CH_2-CH_3), 3.9 (m, 1 H, CHOH), 6.3 (s, 1 H, CH=C), 7.3 (m, 5 H, C_6H_5); ^{13}C NMR δ 10.1, 15.4, 23.1 (t, $^3J_{CF}$= 3 Hz), 68.6, 73. 0 (t, $^2J_{CF}$= 28 Hz, CHOH-CF_2), 116.3 (t, $^3J_{CF}$ = 6 Hz, CH=CCF_2), 119.1 (t, $^1J_{CF}$ = 249 Hz, CF_2-), 124.3, 127.8, 128.3, 128.9, 138.4, 147.6 (t, $^2J_{CF}$ = 25 Hz, CH=C-CF_2). MS: m/e (rel. intensity): 256 (70, M), 198 (15), 170 (10), 101 (40), 90 (100), 77 (40).

Same reaction from silane **2b** (100 mg) provided alcohol **4b** (47 mg, 49 %). ^{19}F NMR δ -112.8 (dt, $^2J_{FF}$ = 251 Hz, $^3J_{FH}$ = 8.5 Hz, 1 F), -114.1 (dt, $^2J_{FF}$ = 251 Hz, $^3J_{FH}$ = 10 Hz, 1F); ^1H NMR δ 0.9 (t, J = 7 Hz, 3 H, CH_3-CH_2), 1.2 (t, J = 7 Hz, 3 H, CH_3-CH_2), 1.4 (m, 2 H), 2.45 (m, 2 H), 2.75 (t, J = 7 Hz, 2 H, CH_2-C_6H_5), 3.70 (q, J = 7 Hz, O-CH_2), 3.75 (m, 1 H, CHOH), 5.5 (t, J = 7 Hz, 1 H, CH=C), 7.2 (m, 5 H, C_6H_5).

(22) Bégué, J.P.; Bonnet-Delpon, D.; Sdassi, H. *Tetrahedron Lett.* **1992**, *33*, 1879-1882. Bégué, J.P.; Bonnet-Delpon, D.; Fischer-Durand, N.; Reboud-Raveaux, M.; Amour, A. *Tetrahedron Asymmetry* **1994**, *5*, 1099-1110. Bégué, J.P.; Bonnet-Delpon, D. in *Biomedical Frontiers of Fluorine Chemistry*, ACS Symp. Ser. vol. 639, Ojima, I.; McCarthy, J.R.; Welch, J.T. Eds, Washington DC, Chapter 4, 1996, pp 59-72.