41. Fluorine-Containing Organozinc Reagents

Part III[1])

A New Formylation Reaction of Fluoroalkylzinc Halides[2])

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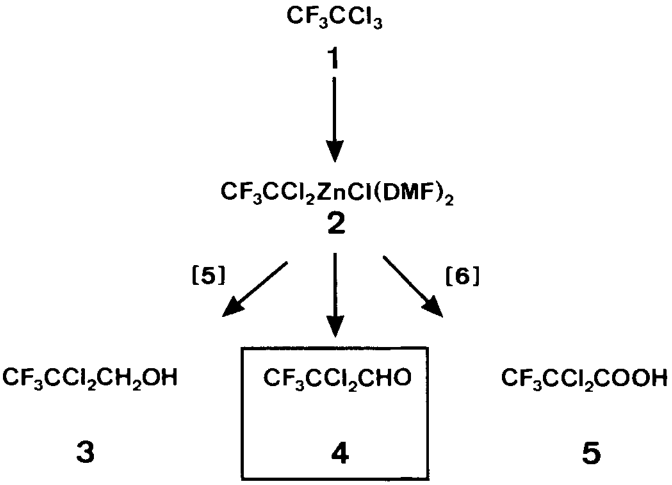
A new Si-induced *Vilsmeier*-type formylation of F-containing organozinc reagents is described. This two-step process *via* the isolable intermediate **10** seems to be quite general for the synthesis of anhydrous polyhalogenated aldehydes.

Various polyfluorinated hydrocarbons are excellent starting materials for the preparation of versatile F-containing synthetic building blocks [2]. In particular, a simple synthesis of CF_3CCl_2-substituted alcohols [3] [4] prompted us to further elucidate the Zn-induced addition of 1,1,1-trichloro-2,2,2-trifluoroethane (CF_3CCl_3, **1**) to electrophilic C-centers. After isolation and characterization of the key intermediate **2** [1] and its successful addition to both aldehydes [5] and CO_2 [6], we were finally looking for an appropriate formylation reaction to generate directly the still missing oxidation state of the aldehyde **4** (*Scheme 1*).

Scheme 1



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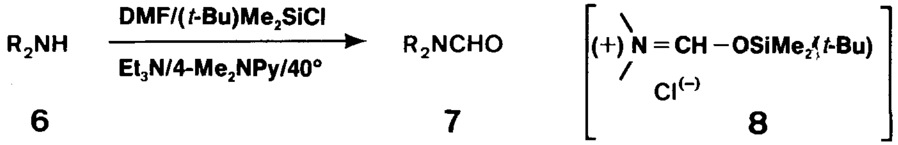
[1]) Part II: [1].

[2]) Presented in part at the 'Autumn Meeting of the Swiss Chemical Society', October 16, 1987, the University of Berne.

In our hands, all attempts to prepare aldehyde **4** by reacting reagent **2** with those formylating agents which are normally effective with *Grignard* and organolithium reagents [7] have failed. Additionally, neither the alcohol **3** by any oxidation procedure nor the carboxylic acid **5** by various reduction methods could be transformed in an easy way to **4**. The *Rosenmund* reduction of acyl halides, *e.g.*, works only well when the α-halogen atoms are F-atoms, whereas the $LiAlH_4$ reduction of the corresponding carboxylic esters seems to be a hazardous reaction.

In a recent publication, *Djurič* has described an interesting formylation of secondary amines **6** by using DMF in the presence of (*tert*-butyl)chlorodimethylsilane [8] *(Scheme 2)*. The author gave some evidence that this particular reaction might proceed through a *Vilsmeier*-type intermediate **8**.

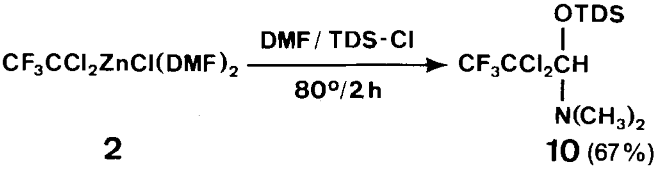
Scheme 2



$$\underset{\mathbf{6}}{R_2NH} \xrightarrow[Et_3N/4\text{-}Me_2NPy/40°]{DMF/(t\text{-}Bu)Me_2SiCl} \underset{\mathbf{7}}{R_2NCHO} \qquad \underset{\mathbf{8}}{\left[\,(+)\,N=CH-OSiMe_2(t\text{-}Bu)\ \ Cl^{(-)}\right]}$$

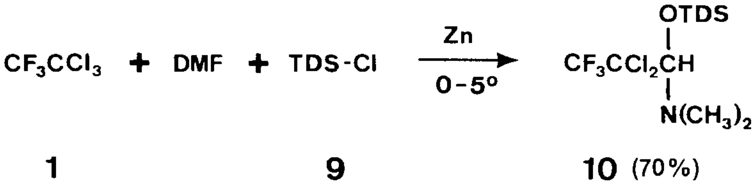
Similarly, when the DMF complex **2** is heated for 2 h in the presence of an equimolar amount of chlorodimethyl(thexyl)silane (= chlorodimethyl(2,3-dimethylbutan-2-yl)-silane; TDS-Cl; **9**) in DMF at 80°, the reasonably stable hemiaminal **10** is isolated in 67% yield *(Scheme 3)*. This seems to be in perfect accordance with the first step of the *Vilsmeier* reaction pathway reported by *Djurič*. Our efforts to improve the synthetic value of this particular reaction by an *in-situ* process led to a remarkable observation. In contrast to the conditions of reacting the isolated complex **2** as described above, cooling of the *in-situ* process was necessary to prevent overreduction during a markedly exothermic formation of hemiaminal **10** *(Scheme 4)*. Even though *Vilsmeier*-type intermediates

Scheme 3



$$\underset{\mathbf{2}}{CF_3CCl_2ZnCl(DMF)_2} \xrightarrow[80°/2h]{DMF/TDS\text{-}Cl} \underset{\mathbf{10}\ (67\%)}{CF_3CCl_2\overset{\displaystyle OTDS}{\overset{|}{\underset{\underset{\displaystyle N(CH_3)_2}{|}}{C}}}H}$$

Scheme 4



$$\underset{\mathbf{1}}{CF_3CCl_3} + DMF + \underset{\mathbf{9}}{TDS\text{-}Cl} \xrightarrow[0\text{-}5°]{Zn} \underset{\mathbf{10}\ (70\%)}{CF_3CCl_2\overset{\displaystyle OTDS}{\overset{|}{\underset{\underset{\displaystyle N(CH_3)_2}{|}}{C}}}H}$$

8 are most likely involved, two different reaction mechanisms seem to be operative depending on the applied reaction conditions.

Neither the hemiaminal **10** nor any other equivalent which represents a protected form of the corresponding aldehyde **4** has been synthesized so far by a C–C bond-forming reaction. A single analog which is known for almost twenty years has been prepared by adding dimethyl(trimethylsilyl)amine to chloral [9]. Therefore, we were interested in the scope of this particular Si-induced addition of F-containing organozinc reagents to DMF. A list of representative examples (**10**–**15**) is given in *Table 1* (for a more complete study, *cf.* [10]).

Table 1. *Silicon-Induced Addition of* R_F*-Zn-X to DMF* (see also [10])

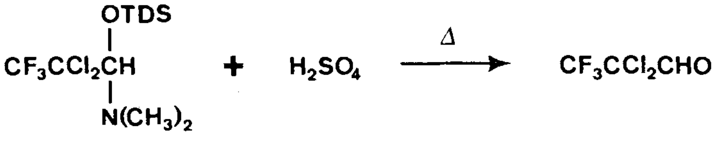
$$R_F\text{-X} + \text{DMF} + \text{TDS-Cl} \xrightarrow{\text{Zn}} R_F\text{-}\underset{\displaystyle N(CH_3)_2}{\overset{\displaystyle OTDS}{CH}}$$

Entry	R_F-X	Reaction conditions	Product (Yield[a]))
a	CF_3I	0°–r.t., 2 h	**11** (74%)
b	CF_3CF_2I	0°–r.t., 2 h	**12** (62%)
c	$CF_3(CF_2)_6I$	0°–r.t., 2 h	**13** (80%)
d	$CFCl_3$	0°–r.t., 2 d	**14** (63%)
e	CF_3CCl_3	0°–r.t., 2 h	**10** (70%)
f	EtOOC–CF_2Cl	80°, 4 h	**15** (84%)

[a]) Non-optimized.

In contrast to the formylation of secondary amines *(Scheme 2)* where the corresponding primary *Vilsmeier* adducts could not be detected [8], a second step was necessary to transform the stable hemiaminal **10**[3]) into the aldehyde **4**. Among other procedures (*cf.* [11]), the use of concentrated sulfuric acid showed to be the method of choice for the preparation of aldehydes of type **4** which in general are known to be quite hygroscopic *(Scheme 5)*.

Scheme 5



$$CF_3CCl_2\underset{\displaystyle N(CH_3)_2}{\overset{\displaystyle OTDS}{CH}} + H_2SO_4 \xrightarrow{\Delta} CF_3CCl_2CHO$$

10 **4** (85%)

According to this two-step process, various well known perhalogenated aldehydes *(Table 2)* which were quite difficult to prepare are now easily accessible in reasonable yields. A direct use of the hemiaminals **10**–**15** *(Table 1)* as stable aldehyde precursors for the synthesis of F-containing molecules of biological interest is currently under investigation.

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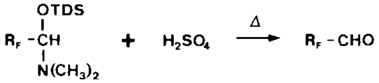
[3]) According to the *in-situ* procedure of *Scheme 4*, **10** can easily be prepared in kg quantities.

Table 2. *Perhalogenated Aldehydes from Hemiaminals* **10–14**



$$R_F\text{-}CH(OTDS)N(CH_3)_2 + H_2SO_4 \xrightarrow{\Delta} R_F\text{-}CHO$$

Entry	Hemiaminal	Aldehyde (Yield[a]))	B.p.[b])	Reference
a	**11**	CF_3CHO (67%)	-18°	[12]
b	**12**	CF_3CF_2CHO (82%)	1.5°	[12]
c	**13**	$CF_3(CF_2)_6CHO$ (75%)	122°	[12]
d	**14**	$CFCl_2CHO$ (76%)	57°	[13]
e	**10**	CF_3CCl_2CHO (85%)	66–67°	[14]

[a]) Non-optimized.
[b]) Under atmospheric pressure.

I am especially indebted to Dr. *Ch. Angst* and to Dr. *H. Greuter* for helpful discussions, and I like to thank Mrs. *A. Ente*, Miss *J. Schaub*, and Miss *A. Stern* for their skillful assistance in the laboratory. I am grateful to my colleagues in the Physical Department for performing the spectral analyses.

Experimental Part

1. *General.* See [4]. Chlorodimethyl(thexyl)silane (TDS-Cl) can be purchased from *Fluka AG*.

2. *Hemiaminals* **10–15**. *Method A.* A mixture of 69.8 g (0.175 mol) of $CF_3CCl_2ZnCl(DMF)_2$ (**2**) [1], and 34.2 g (0.191 mol) of TDS-Cl in 200 ml of DMF was heated for 2 h under Ar at 80°. Then, the cold mixture was extracted with pentane, and the pentane phase washed with H_2O, dried ($MgSO_4$), and evaporated. Distillation of the oily residue at 70°/0.01 Torr afforded 43.1 g (67%) of *2,2-dichloro-1-{[dimethyl(2,3-dimethylbutan-2-yl)silyl]oxy}-3,3,3-trifluoro-*N,N*-dimethylpropylamine* (**10**) as a pale yellow oil. ^{1}H-NMR (250 MHz, $CDCl_3$): 4.72 (*s*, 1 H); 2.53 (*s*, $(CH_3)_2N$); 1.70 (*sept.*, J = 6.5, $(CH_3)_2CH$); 1.10–0.80 (*m*, 4 CH_3); 0.18 (2*s*, $\Delta\delta$ = 0.015, $(CH_3)_2Si$). ^{13}C-NMR ($CDCl_3$): 122.1 (*q*, J(F,C) = 283, CF_3); 90.3 (*s*, CCl_2CH); 88.7 (*q*, J(F,C) = 29, CCl_2CH).

Method B. To a mixture of 20.7 g (0.11 mol) of CF_3CCl_3 (**1**) and 17.8 g (0.10 mol) of TDS-Cl in 100 ml of DMF, 6.8 g (0.10 mol) of freshly activated Zn powder was added under Ar at a rate to maintain the reaction temp. below 5°. Then, the mixture was stirred for 1 h at r.t. whereupon 25.6 g (70%) of **10** could be isolated as described above.

According to *Method B*, the hemiaminals **11–15** (*cf. Table 1*) have been prepared starting from the appropriate commercially available polyhalogenated compounds (R_F-X). Physical data: see *Table 3*.

Table 3. *Physical Data of the Hemiaminals* **11–15**

Entry	Hemiaminal (b.p.)	^{1}H-NMR (250 MHz, $CDCl_3$)[a])	^{13}C-NMR ($CDCl_3$)[b])
a	**11** (50°/0.01 Torr)	4.46 (*q*, J = 5.5, 1 H); 2.40 (*s*, $(CH_3)_2N$)	123.6 (*q*, J(F,C) = 286, CF_3); 85.4 (*q*, J(F,C) = 33, CH)
b	**12** (60°/0.01 Torr)	4.54 (*dd*, J = 10, 10, 1 H); 2.40 (*s*, $(CH_3)_2N$)	125.0 (*m*, CF_3); 84.8 (*dd*, J(F,C) = 22, 22, CH)
c	**13** (80°/0.01 Torr)	4.60 (*t*, J = 11.25, 1 H); 2.41 (*s*, $(CH_3)_2N$)	84.9 (*dd*, J(F,C) = 21, 21, CH)[c])
d	**14** (65°/0.01 Torr)	4.52 (*d*, J = 7, 1 H); 2.52 (*s*, $(CH_3)_2N$)	123.3 (*d*, J(F,C) = 307, $CFCl_2$); 92.8 (*d*, J(F,C) = 26, CH)
e	**15** (90°/0.01 Torr)	4.59 (*dd*, J = 13.5, 13.5, 1 H); 4.30 (*m*, OCH_2CH_3); 2.36 (*s*, $(CH_3)_2N$); 1.33 (*t*, J = 7.5, OCH_2CH_3)	163.9 (*t*, J(F,C) = 32, CO); 114.6 (*dd*, J(F,C) = 255, 255, CF_2); 86.6 (*dd*, J(F,C) = 22, 22, CH)

[a]) The signals for the dimethyl(thexyl)silyl group are omitted.
[b]) Only the signals downfield from $CDCl_3$ are reported here.
[c]) The signals for the perfluoroheptyl chain could not be assigned.

3. *2,2-Dichloro-3,3,3-trifluoropropanal* (**4**). The oily **10** (149 g, 0.5 mol) was added dropwise to conc. H_2SO_4 soln. at 90°. The product which was formed immediately was flushed in a stream of N_2 and frozen in a cold trap. Redistillation of the collected material at 66–67° by using a *Vigreux* column afforded 75 g (83%) of colourless **4**, identical in all physical aspects with the compound reported in [14].

By using the same procedure, all the other well known aldehydes of *Table 2* (*cf.* [12] [13]) were prepared and their physical data compared with those reported.

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