Reaction of C2-Symmetrical Dialkoxysilanes R_1O-$Si(R_2)_2$-OR_1 with the two Vilsmeier-Haack Complexes $POCl_3$·DMF and $(CF_3SO_2)_2O$·DMF: An Efficient One-Step Conversion to the Corresponding Formates R_1-OCHO

Yariv Cohen, Vadim Kotlyar, Sylvain Koeller,[1] Jean-Paul Lellouche*

Department of Chemistry, Bar-Ilan University, Ramat-Gan 52900, Israel
Fax +972(3)5351250; E-mail: lellouj@mail.biu.ac.il

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Abstract: The two electrophilic Vilsmeier-Haack complexes $POCl_3$·DMF **1** and $(CF_3SO_2)_2O$·DMF **2** react with *C2*-symmetrical dialkoxysilanes R_1O-$Si(R_2)_2$-OR_1 (R_1 = (-)-menthyl or 3β-cholesteryl, R_2 = Me, Ph or *i*-Pr: **5a-c/6a-c**) affording the formates R_1-OCHO **7** and **8** in medium to good yields depending on conditions. The scope and limitations of this novel one-step deprotection of *C2*-symmetrical silaketals to formates are described.

Key words: Vilsmeier-Haack complexes, protecting group interconversion, deprotection, formates, formylation

Reacting pre-organized species intramolecularly using a neutral and removable "silicon temporary connection" has been developed quite successfully in various fields of synthetic organic chemistry.[2–4] Expectedly, the intramolecular character of this process involving silaketals of the type R_1O-$Si(R_2)_2$-OR_3 would allow an enhanced predictable control of the attachment regio- and stereoselectivity. Significant examples can be found in the recent literature dealing with glycosidation,[5–7] with ring-closure metathesis,[8–10] with [4+2]-Diels–Alder reactions,[11–14] with photochemical ene-ene or ene-yne [2+2]-cycloadditions,[15–17] with azomethine ylide [3+2]-cycloadditions,[18,19] with [3+2]-nitrone cycloadditions,[20] with benzoannulation reactions of chromium siloxycarbene complexes,[21] with Pd-catalyzed Heck reactions,[22] and with radical cyclizations.[23–27] Following reaction, resulting cyclic *O*-silylated diethers must be further manipulated to eliminate the silicon tether and liberate the latent OH-functionalities. The conditions needed for that may not always be compatible with other functional groups present.

Synthetically speaking, the overall concept would be even more attractive if a non-fluoride-based elimination of the silyl tether were available to liberate *O*-protected rather than OH-products, in only one-step. This approach would save synthetic steps with the potential advantage of increasing overall yield. During recent exploratory works on glycal-based peptidomimetics, we discovered that the two electrophilic Vilsmeier-Haack (VH) complexes $POCl_3$·DMF **1** (equilibrium mixture of the two salts **3** and **4**, Scheme 1) and $(CF_3SO_2)_2O$·DMF **2**[28,29] are able to mediate the one-step conversion of diverse *O*-TES/*O*-TBDMS/*O*-TIPS/*O*-TBDPS ethers R_4-$OSi(R_5)_3$ to the corresponding formates R_4-OCHO (anhydrous DMF, 0 °C to 20 °C, yield range 50-91%).[30,31] This mild one-step interconversion of OH-protecting groups would fulfill the above requirement if applicable to both alkoxy groups of alkoxysilanes. As simple models, we first investigated the easily accessible *C2*-symmetrical dialkoxysilanes R_1O-$Si(R_2)_2$-OR_1. *Interestingly and to the best of our knowledge, no similar conversion has been reported in the current literature*.

We hereby report our findings, emphasizing the scope and limitations of this unique and mild transformation.

The symmetrical (–)-menthol- and 3β-cholesterol-based dialkoxysilanes **5a-c** and **6a-c** were prepared uneventfully using the Hanessian's silylation conditions (anhydrous DMF, imidazole, appropriate dichlorosilane: 2.1 equiv., 0–20 °C, 18 h, unoptimized yields of purified substrates 36-96%, Scheme 1 and Table).[32] Different silyl connectors (R_2 = Me, Ph and *i*-Pr) were included in our reactivity studies to provide information regarding the influence of growing steric hindrance at silicon. The two electrophilic VH-complexes **1** and **2** were prepared classically by slow addition of freshly distilled $POCl_3$ or $(CF_3SO_2)_2O$ to anhydrous DMF under nitrogen at 0 °C and stirring over 30 min at this temperature. The complexes were then immediately reacted with the model dialkoxysilanes **5a-c/6a-c** following the reported protocol[35] and subsequent modifications registered in the Table of results. Furthermore, the influence of different molar ratios between the VH-complexes and substrates (**1** or **2** *versus* **5a-c** or **6a-c**, molar equivalents: 0.3/1.0, 1.0/1.0 and 2.0/1.0) has been examined.

Several valuable conclusions may be drawn (Scheme 1 and Table). As expected, the *O*-formylation of the dialkoxysilanes **5a-c** and **6a-c** may be operated under mild conditions leading to the formates **7** and **8**, using either of the two VH-complexes **1** or **2** (entries 4-9 and 10-15, see also the general *O*-formylation protocol).[35] Depending on the VH-complex, conversion yields vary in a low/medium (20-78%, **2**: entries 4-9, 10-14) to good range (≥ 80%, **1**: entries 5-7, 9-10, and 15). Uniformly, unreacted starting material and/or hydrolyzed (–)-menthol/3β-cholesterol accounts for mass balance. Almost under all conditions, the VH-complex **1** is the more efficient (entries 4-12 and 14-15). Except for one entry (entry 13), this same reactivity feature is observed for any molar ratio, 1.0/1.0 or 2.0/

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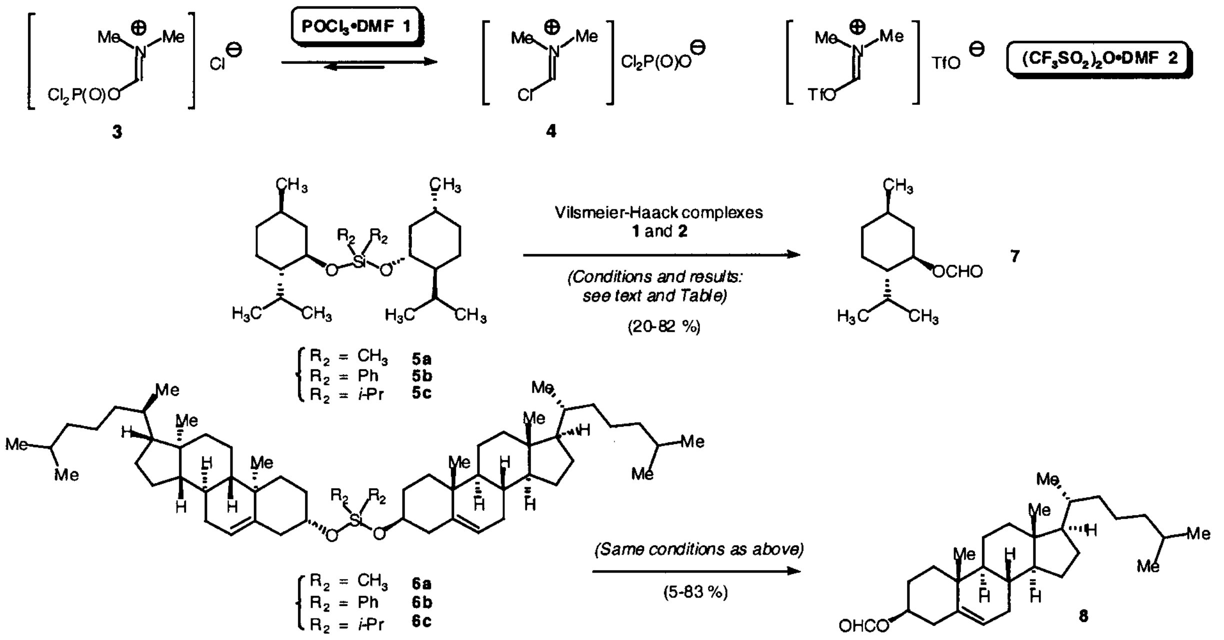


Scheme 1

Table Reaction of Dialkoxysilanes R_1O-$Si(R_2)_2$-OR_1 with the VH-Complexes $POCl_3$·DMF **1** and $(CF_3SO_2)_2O$·DMF **2**

Entry	Substrate (1.0 equiv.)	$POCl_3$·DMF **1** or $(CF_3SO_2)_2O$·DMF **2** (equiv.)[b]	Formate **7**		Formate **8**	
			1: (%)[a,c]	**2**: (%)[a,c]	**1**: (%)[a,c]	**2**: (%)[a,c]
1	**5a**	0.3	42	–	–	–
2	**5b**	″	38	–	–	–
3	**5c**	2	22	–	–	–
4	**5a**	1.0	73	20	–	–
5	**5b**	″	80	30	–	–
6	**5c**	2	80	36	–	–
7	**5a**	2.0	82	68	–	–
8	**5b**	″	77	56	–	–
9	**5c**	2	82	66	–	–
10	**6a**	1.0	–	–	82	50
11	**6b**	″	–	–	75	50
12	**6c**	2	–	–	46	30
13	**6a**	2.0	–	–	75	78
14	**6b**	″	–	–	76	59
15	**6c**	″	–	–	83	5

[a] Yields of isolated purified compounds.

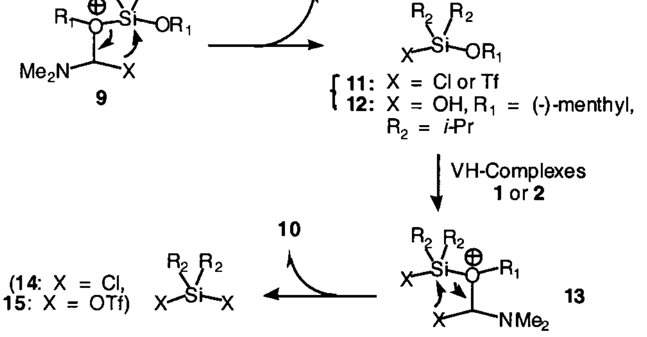
[b] Number of molar equivalents *versus* substrate (1.0 equiv.).

[c] Averaged yields for at least two trials except for entries 1 and 15 (VH-complex **2**) (3 trials).

1.0, between VH-complexes and starting dialkoxysilanes (1.0/1.0, entries 4-6 and 10-12; 2.0/1.0: entries 7-9 and 14-15). Thus, although it is the more electrophilic, since it is capable of formylating electronically deficient aromatics,[33] the VH-complex **2** does not follow the efficiency trend observed for the *O*-formylation of simple *O*-silylated ethers by the same VH-complexes.[31] Regarding reagent **1**, comparison of entries 4-6 and 10-11 (ratio 1.0/10: 73-82%) *versus* entries 7-9 and 13-15 (2.0/1.0: 75-83%) shows that conversion yields are very similar for those two different ratios. It seems likely that, at least, one another VH-reagent, different from **1**, has been generated able of the same conversion. This unexpected result needs clarification and will be the object of future works. Interestingly, when the VH-complex **2** is used in a 1.0/1.0 molar ratio, the two formates are obtained in yields inferior or equal to 50% (Table, entries 4-6 and 10-12: 20-50%).

In the case of the VH-complex **1** and, except for the result of entry 12, increasing steric hindrance at silicon in **5a-c/6a-c** (R_2 = Me, Ph and *i*-Pr) has no major effect on the transformation yields (entries 4-9: 73-82%; entries 10-11 and 13-15: 75-83%). Again, this reactivity trend differs fundamentally from previous data obtained with the similar *O*-formylation of simple *O*-silylated ethers.[30,31] On the contrary, marginal steric effect can be detected when the VH-reagent **1** is reacted with **5a-c** in a sub-molar ratio (0.3/1.0, entries 1-3: 22-42%). The following scaling of steric hindrance at silicon Me << Ph << *i*-Pr has been found.

Using authentic material obtained by a different route,[30] high-field $^1H/^{13}C$ NMR spectroscopies ($CDCl_3$, 300 MHz and 75 MHz) and TLC confirm retention of configuration for **7** and **8**.



Scheme 2

A stepwise mechanism appears likely in view of some previous results.[30,31] The electrophilic VH-complexes **1** or **2** can add the dialkoxysilanes **5a-c/6a-c** affording the oxonium cation **9** (first Si-O bond, Scheme 2). Thermodynamically strong Si-Cl/Si-O bonds (111.0 kcal/mole and 128.2 kcal/mole),[34] favor its decomposition toward the neutral species $R_1O\text{-}Si(R_2)_2\text{-}X$ **11** (X = Cl or TfO) and the imidate salt **10** (first equiv.). Subsequent hydrolysis of **10** furnishes the formates **7-8**. The second Si-O bond in the silylated intermediate **11** can react similarly, giving a second equivalent of the same imidate **10** accompanied respectively by the dichlorosilane or bistriflated silane **14** or **15**. Indirect evidence is afforded by two observations. First, it has been possible to isolate and partially characterize the chromatographically labile silanol ether **12** (Table, entry 9, VH-complex **1**, R_1 = (–)-menthyl, R_2 = *i*-Pr) implying the hydrolysis of the intermediate **11** (high-field ^1H NMR, 300 MHz, $CDCl_3$; EI-MS/DCI-MS (NH_3 and CH_4)). Moreover, depending on the VH-complex, the second step **11** → **13** should be disfavored when involving a less nucleophilic intermediate **11** (X = OTf) *versus* **11** (X = Cl). Indeed, this factor rationalizes well the marked difference of conversion efficiency observed for **1** and **2**.

In conclusion, we have demonstrated that the two VH-complexes **1** and **2** can react cleanly with *C2*-symmetrical dialkoxysilanes $R_1O\text{-}Si(R_2)_2\text{-}OR_1$ affording the corresponding formates R_1-OCHO in low/medium to high yields depending on conditions and substrates. In any case, the VH-complex **1** is the most efficient reagent to perform this mild one-step transformation, which, interestingly, is rather insensitive to steric hindrance at silicon.[35,36]

References and Notes

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(35) **Representative experimental protocol (exemplified for a 1.0/1.0 ratio between VH-reagents and substrates).** Freshly distilled phosphorus oxychloride $POCl_3$ or triflic anhydride Tf_2O (1.0 mmol) was dissolved in cooled anhydrous DMF (1.0 mL, –5 °C) under nitrogen, and agitated for 30 min at the same temperature affording a homogeneous DMF solution of the two VH-reagents **1** and **2** for immediate use. Depending on conditions (Table), the VH-reagent was added dropwise to a cold solution of the requisite substrate **5a-c/6a-c** (1.0 mmol, 1.0 mL of anhydrous DMF, –5 °C). The medium was stirred overnight at 20 °C. After medium hydrolysis at –5 °C (saturated aqueous solution of $NaHCO_3$, 10 mL), the aqueous layer was extracted with ether (4 × 10 mL). The combined organic layers are washed to neutrality with water (2 × 10 mL), dried over anhydrous $MgSO_4$, filtered (5 µm Buchner filter)and evaporated under reduced pressure. The resulting crude formates are purified by preparative flash chromatography on a silica gel column (silica gel Merck Si-60, 43-60 µm) eluted by a hexane–CH_2Cl_2, 60:40 mixture. They are obtained as an homogeneous pale oil (**7**) or solid (**8**) (reaction conditions and yields are registered in the Table).

(36) The new compounds have been fully characterized spectroscopically (FT-IR, $^1H/^{13}C$ NMR, EI/DCI-MS) and their homogeneities checked by TLC and/or HPLC.