The Particular Sensitivity of Silyl Ethers of D-Glucal toward Two Vilsmeier−Haack Reagents $POCl_3$·DMF and $(CF_3SO_2)_2O$·DMF. Their Unique and Selective Conversion to the Corresponding C(6)-*O*-Formates

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The two electrophilic Vilsmeier−Haack reagents $POCl_3$·DMF **2** or $(CF_3SO_2)_2O$·DMF **3** mediate the *one-step and selective* conversion of *O*-triethylsilyl (*O*-TES), *O*-*tert*-butyldimethylsilyl (*O*-TBDMS), *O*-*tert*-butyldiphenylsilyl (*O*-TBDPS), and *O*-triisopropylsilyl (*O*-TIPS) ethers of D-glucal to the corresponding C(6)-*O*-formates.

Introduction

Silyl ethers RO−SiR′$_3$ **1** have become the most popular protecting groups for hydroxyl functions during complex multistep syntheses, especially when orthogonal protective/deprotective steps are required.[1,2] These ethers display a unique set of properties, ranging from their easy introduction, through their good stability over a wide range of conditions, to the variety of their one-step deprotections by well-known fluoride-based, basic/acidic or strongly oxidizing/reducing reagents.[1,2] Nevertheless, if performed on multifunctional or sensitive molecules, one-step *O*-silyl ether deprotections may be problematic, requiring milder conditions.[3,4] Alternatively, innovative two-step procedures interconverting **1** to a different kind of protected ether RO−Pg (Pg: protecting group) followed by smooth hydrolysis of the Pg (RO−SiR′$_3$ → RO−Pg → ROH) could be also of interest, each approach possessing its particular advantages and limitations.

On the basis of these considerations, we very recently performed some preliminary experiments on the neutral one-step transformation of *O*-TBDMS/*O*-TES ethers of type **1** (R alkyl residue, Scheme 1) to their corresponding formates RO−CHO **7**, promoted by the Vilsmeier−Haack reagent $POCl_3$·DMF **2**[5,6] (equilibrium mixture of the two salts **8** and **9**, Figure 1 and Scheme 1: anhydrous DMF, 0 °C to 20 °C, yield range: 62−98%).[7] A likely mechanism is addition of the Vilsmeier−Haack reagent **2** to the silyl ether **1** to afford the intermediate oxonium cations **4a** (mixture of Cl^- and/or $Cl_2P(O)O^-$ counteranions). Due to the formation of the thermodynamically strong Si−Cl/Si−O bonds (111.0 and 128.2 kcal, respectively),[8] the elimination of the neutral species R′$_3$Si-X$_1$ **5a** (R′$_3$Si = TES or TBDMS, X$_1$ = Cl and/or O(O)PCl$_2$) generates in situ the related imidate salts **6a** (mixture of same counteranions), whose subsequent smooth hydrolysis affords the corresponding formate **7**. To the best of our knowledge, only very few OH-protecting group exchange reactions are known, none affording formates from silyl ethers, as described above.[9a−h] Consequently, considering the easy and high-yielding deprotection of formates,[1] such an OH-protecting group interconversion R−OTBDMS/R−OTES → R−OCHO could constitute the first step of an innovative two-step deprotection variant of **1**, provided that it could be generalized to other kinds of *O*-silyl ethers and, preferably, multifunctional ones.

The purpose of this communication is to report our recent results generalizing this one-step conversion promoted by the Vilsmeier−Haack reagent **2** (RO−SiR′$_3$ **1** → RO−CHO **7**, various R and R′, Schemes 1−3 and Table 1). The second more electrophilic Vilsmeier−Haack complex $(CF_3SO_2)_2O$·DMF **3** (Figure 1), known to be superior in the formylation of electronically deficient

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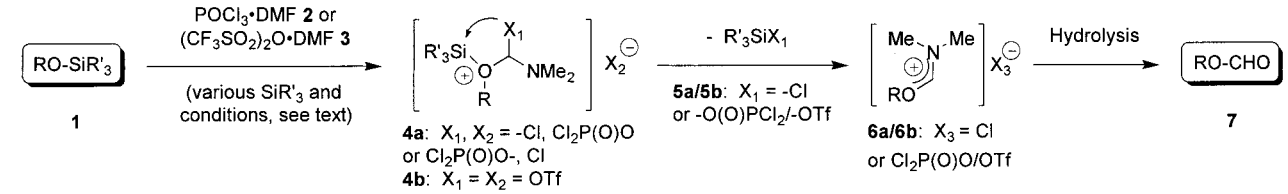
Scheme 1. One-Step Conversion of *O*-Silyl Ethers 1 to the Corresponding Formates 7



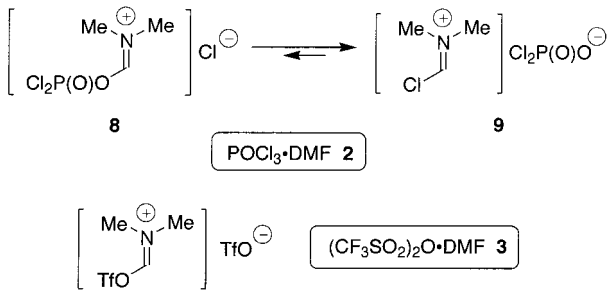


Figure 1. Vilsmeier−Haack complexes **2** and **3**.

aromatics,[10] was also capable of promoting this transformation, but with reactivity trends slightly different from those of **2**, depending on the substrates and conditions. In this study, the densely functionalized *O*-silylated D-glucal-based precursors **12**−**15**, **20**−**23**, and **25** were used as model compounds to explore the scope and some of the limitations of this transformation (Schemes 1−3). The main premises that guided our substrate design were that (1) these sugar cyclic enol ethers are mostly acid-sensitive, (2) these enol ethers contain, on the same unsaturated cyclic carbon skeleton, a dense array of *O*-silyl ethers of primary, secondary/secondary allylic nature in 1,2-/1,3-/1,4-relationships, and therefore provide different reactivities, and (3) the particular substrates **12**−**15** and **20**−**23** can be used to test the *C*-formylation of their intracyclic enol ether functions to afford C(2)−CHO compounds of type **24** which, potentially, should compete with the expected *O*-formylation (Scheme 2).[11]

Results and Discussion

Preparation of the *O*-Silylated Substrates 12−15, 20−23, and 25. The preparation of the required *O*-silylated D-glucal-based precursors **12**−**15**, **20**−**23**, and **25** began from D-glucal **10**, obtained by basic methanolysis of tri-*O*-acetyl-D-glucal (catalytic MeONa, MeOH, 0−20 °C, quantitative yield) or from the known tri-*O*-benzyl-D-glucal **11**[12] (Scheme 2). The carbohydrate **10** could be either persilylated or selectively silylated at its primary C(6)−OH with different chlorosilanes having various degrees of steric hindrance, such as TES−Cl, TBDMS−Cl, TBDPS−Cl, and TIPS−Cl (classical Hanessian's silylation protocol: chlorosilane: 1.0 or 3.3 equiv, depending on substrates, imidazole, anhydrous DMF, 20 °C or − 18 °C, 14 h).[13] The fully and partially *O*-silylated compounds **12**−**15** and **16**−**19**, respectively, were obtained in a 44−99% yield range. The C(6)-*O*-silylated precursors **16**−**19** could be further benzylated to the *O*-silylated-3,4-di-*O*-benzyl-substrates **20**−**23** (NaH, anhydrous THF, BnBr, catalytic nBu$_4$NI, 0−20 °C, 24 h, 37−86% nonoptimized yields). The presence of a catalytic amount of nBu$_4$NI in the medium (10% molar) was an absolute requirement for supressing base-mediated inter- or intramolecular silyl group migrations to give the observed regioselective C(3)−OH/C(4)−OH-benzylation.[14] Furthermore, the C(2) regioselective Vilsmeier−Haack formylation of tri-*O*-benzyl-D-glucal **11** by reagents **2** or **3**, followed by the chemoselective reduction of the resulting enal **24** (anhydrous DMF, 0−20 °C, overnight, **2**: 60%, **3**: 70%; NaBH$_4$, MeOH, 20 °C, 20 min, 85%), afforded the 2-hydroxymethyl-3,4,6-tri-*O*-benzyl-D-glucal,[11,15] as the appropriate precursor of the allylic *O*-TBDMS ether **25** (same silylation protocol as that given above using TBDMS−Cl, 90%, 46−54% overall yield from **11**). Worthy of mention is the fact that, for the first time, reagent **3** was shown to formylate the sugar cyclic enol ether **11** with the same regioselectivity as **2**, but in a better yield (**2** and **3**: 60% and 70%).

Reaction of the Vilsmeier−Haack Reagents POCl$_3$·DMF 2 and (CF$_3$SO$_2$)$_2$O·DMF 3 with *O*-Silylated Substrates 12−15, 20−23, and 25. Having multifunctional tri- and mono-*O*-silylated substrates **12**−**15**, **20**−**23**, and **25** at our disposal, we compared their reactivities toward the Vilsmeier−Haack reagents POCl$_3$·DMF **2** or (CF$_3$SO$_2$)$_2$O·DMF **3** with the aim of revealing the synthetic generality and the limits of this one-step OH-protecting group interconversion (Scheme 3 and Table 1; see the Supplementary Information for detailed general experimental procedures). The electrophilic reagents **2** and **3** are classically prepared in situ by slow addition of POCl$_3$ or (CF$_3$SO$_2$)$_2$O in anhydrous DMF under nitrogen at 0 °C and agitation over 30 min at same temperature. For all the *O*-silylated substrates under consideration, reagents **2** and **3** were used in a slight excess (10% molar) per *O*-silylated function (**12**−**15**: 1.0 mmol, **2**/**3**: 3.3 equiv, 5.0 mL of DMF; **20**−**23** and **25**: 1.0 mmol, **2**/**3**: 1.1 equiv, 3.0 mL of DMF).

From the results given in Table 1, several valuable conclusions may be drawn:

1. Irrespective of the silylation pattern of silyl groups present in the substrates **13**−**15** and **20**−**23**, the expected *O*-formylation was promoted by reagents **2** and **3**, affording the corresponding formates **27**−**30** in a medium- to high-yield range (entries 3−5 and 7−10, 50−91%). More particularly, reagent **3** was more reactive than **2** to formylate the tri-*O*-TBDMS substrate **13** (entry 3: 8 h versus 6 h) for similar yields in **27** (70−69%). Slightly improving the yield, the same reactivity trend was observed for the addition of anhydrous pyridine (3.3 equiv/**13**, entries 3 versus 4: 8 h-70%/72 h-80% and 6

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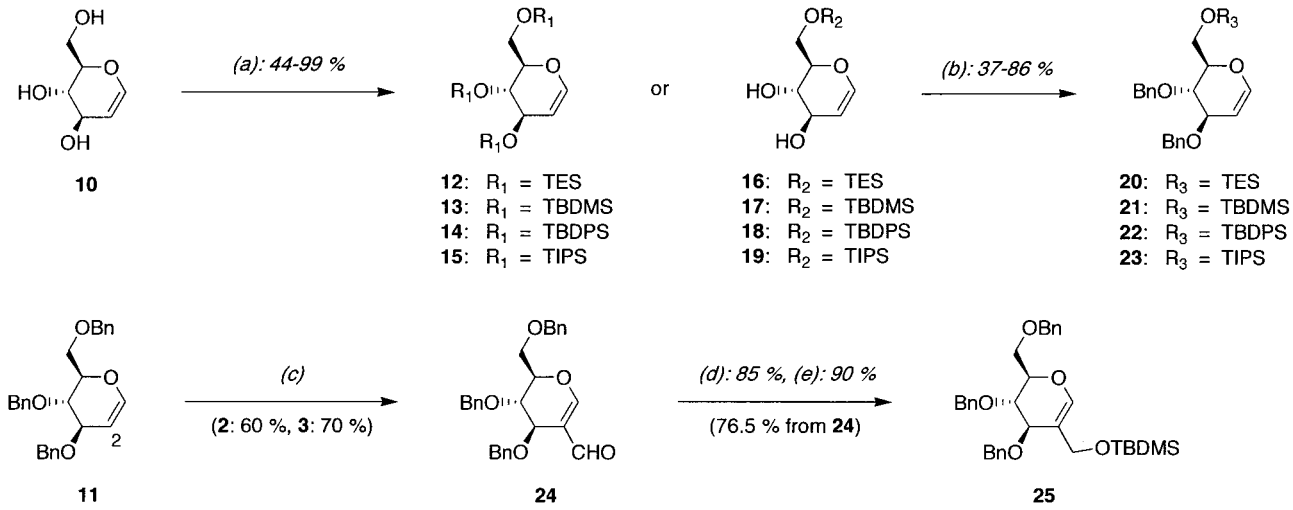
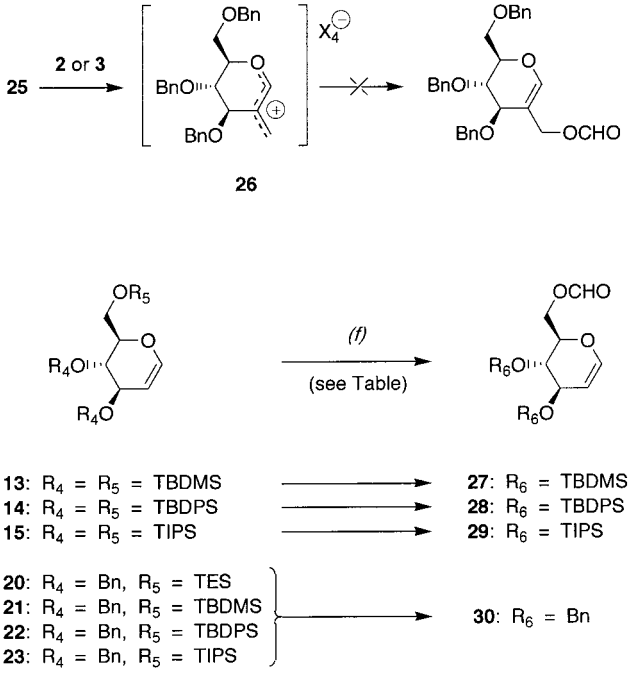
Scheme 2.[a] Preparation of *O*-Silylated D-Glucal-Based Substrates **12**−**15**, **20**−**23**, and **25**



[a] Key: *(a)* chlorosilane (1.0 or 3.3 equiv/**10**, see text and Supporting Information), imidazole, anhydrous DMF, 20 °C (**12**−**15**) or − 18 °C (**16**−**19**), 14 h; *(b)* NaH, anhydrous THF, cat. *n*Bu_4NI, BnBr, 0 °C to 20 °C, 24 h; *(c)* $POCl_3$·DMF **2** or $(CF_3SO_2)_2O$·DMF **3**, anhydrous DMF, 0 °C to 20 °C, overnight; *(d)* $NaBH_4$, EtOH, 20 °C, 20 min; *(e)* TBDMS−Cl, imidazole, anhydrous DMF, 20 °C, 14 h.

Scheme 3[a]



[a] Key: *(f)* $POCl_3$·DMF **2** or $(CF_3SO_2)_2O$·DMF **3**, anhydrous DMF, 0 °C to 20 °C.

Table 1. Reaction of Vilsmeier−Haack Reagents 2 and 3 with *O*-Silylated D-Glucal Derivatives 12−15, 20−23, and 25

entry	precursor	product (R_6)	reagent **2** [(%)[a], (h)[b]]		reagent **3** [(%)[a], (h)[b]]	
1	**12**	−	-	0.5[c]	−	0.5[c]
2	**12**	−	-	0.5[d]	−	0.5[d]
3	**13**	**27** (TBDMS)	70	8	69	6
4	**13**	**27** (TBDMS)	80[d]	72	78[d]	48
5	**14**	**28** (TBDPS)	50	8	65	8
6	**15**	**29** (TIPS)	5−10	48	5−10	48
7	**20**	**30** (Bn)	70	3	84	2
8	**21**	**30** (Bn)	82	4.5	85	3.5
9	**22**	**30** (Bn)	60	24	70	8
10	**23**	**30** (Bn)	85	8	91	8
11	**25**	−	−	0.5[c,d]	−	0.5[c,d]
12	**27**	no reaction	−	4.5	−	4.5
13	**30**	no reaction	−	24	−	24

[a] Yields of isolated purified compounds. [b] Reaction time for substrate consumption (TLC check). [c] The starting glucal derivative is consumed without formation of any formate. [d] Anhydrous pyridine (1.1 equiv. per *O*-silyl function) is added to Vilsmeier−Haack complex prior to the glucal derivative.

h-69%/48 h-78%). Moreover, the tri-*O*-TBDPS-precursor **14** was more efficiently converted to the corresponding formate **28** by the more electrophilic **3** (entry 5: 50% and 65%). Analogous conclusions about the comparative reactivity and synthetic efficiency of **3** versus **2** may be drawn for the second series of *O(6)*-silylated-3,4-di-*O*-benzyl-substrates **20**−**23** (entries 7−10). Yields of the *O-(6)*-formate **30** were systematically higher with **3** than with **2**, while, in parallel, reaction times to completion were reduced. Interestingly, the silyl groups in **20**−**23** can be graded by their decreasing *O(6)*-formylation reactivity toward **2** and **3**, as follows, **2**: TES ≫ TBDMS ≫ TIPS ≫ TBDPS and **3**: TES ≫ TBDMS ≫ TBDPS ∼ TIPS. This reactivity scale roughly follows increasing steric hindrance at silicon.

Interestingly, the dense and varied protection pattern of C(3)/C(4)-hydroxyl groups in substrates **15** and **23** (*O*-Bn versus *O*-TIPS groups) drastically modified the course of formylation. Indeed, the TIPS OH-protecting group in **15** can be considered stable toward **2** and **3**, since less than 5−10% conversion to the corresponding C(6)-*O*-formate **29** was observed in 48 h (entry 6). In contrast, the sterically less encumbered 6-*O*-triisopropylsilyl-3,4-di-*O*-benzyl-D-glucal **23** afforded the expected C(6)-*O*-formate **30** in very good yields (entry 10, **2** and **3**: 8 h, 85% and 91%).

Relative to substrates **13**−**14** and **20**−**23**, the presence of the strong Lewis acids $R'_3Si-OTf$ in the medium compared to that of the neutral species R'_3Si-X_1 (X_1 = $Cl/O(O)PCl_2$), respectively generated from reagents **3** and **2**, does not seem particularly detrimental to the conversion.

2. Some limitations for this conversion have been encountered. For example, the tri-*O*-TES-D-glucal **12** was destroyed in less than 30 min when reacted with **2** or **3** (TLC check, entry 1). Similarly, since involving the highly stabilized carbocation **26** (Scheme 3), the same result was

obtained with the extremely acid-sensitive substrate **25** (entry 11). Even the reaction in the presence of anhydrous pyridine (3.3 equiv/**12** and 1.1 equiv/**25**) to quench adventitious acids followed the same trend (entries 2 and 11).

3. Particularly striking in the case of the tri-*O*-silylated substrates **13**−**15**, was the exquisite regioselectivity of *O*-formylation, affording the C(6)-*O*-formates **27**−**29**, since only the primary C(6)-*O*-silylated function was formylated versus the other allylic functions (entries 3−5, 50−80% yield). This selectivity feature was found for both Vilsmeier−Haack reagents in a similar yield range (**2**: 50−80%, **3**: 65−78%). FT-IR and $^{1}H/^{13}C$ NMR data were in good agreement with the depicted structures ($\nu_{O-C=O}$: 1716−1792 cm^{-1}, δ_{CHO} and δ_{CHO} (500 and 50 MHz, $CDCl_3$): 7.98−8.09 ppm, singlet and 160.5−160.8 ppm). In addition, the $H_{6,6'}$ protons in **27**−**29** were strongly deshielded by the C(6)-formate group, in comparison with the respective substrates **13**−**15** (see the relevant spectroscopic data in the Supporting Information).

4. The observed selectivity supports the involvement of a common intermediate salt of type **6a/6b**, that contains a positively charged imidate function formed solely at the C(6)-primary position because of steric reasons (Scheme 1). Even in the presence of a 2-fold excess of **2** or **3**, this imidate function critically positioned at C(6) electronically "disarms" the D-glucal-based intermediates **6a/6b** toward further electrophilic attack of any additional Si−O bonds.[16,17] The same reasoning explains why glucal-based unsaturated aldehydes of type **24** arising from the C(2)-formylation of substrates **13**−**15** and **20**−**23** by **2** and **3** could not be isolated, as depicted previously for structurally similar compounds (entries 3−5 and 7−10).[11] Worthy of mention also is the lack of additional *O*- or *C(2)*-formylation of the C(6)-*O*-formylated-substrates **27** and **30** possessing an electron-withdrawing formyl group at the same critical C(6) primary position (entries 12 and 13).

In conclusion, we demonstrated that *O*-TES, *O*-TBDMS, *O*-TBDPS, and *O*-TIPS silyl ethers of D-glucal are quite sensitive to the two electrophilic Vilsmeier−Haack reagents $POCl_3$·DMF **2** or $(CF_3SO_2)_2O$·DMF **3** being converted *in one step and selectively* to the corresponding C(6)-*O*-formates. The reactivity trends of these two reagents as well as the scope and some limitations of this OH-protecting group interconversion were examined. Additionally, since formates of (−)-menthol and *3β*-cholesterol have been deprotected in mild conditions known to be compatible with *O*-silyl ethers (0.6 M NH_4OH in MeOH, 20 °C),[1,7] this transformation will allow the straight preparation of differentially protected D-glucal derivatives.

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Supporting Information Available: Detailed experimental procedures (including references for each known compounds) for the preparation of *O*-silylated precursors **12**−**15**, **20**−**23**, and **25** and corresponding formates **27**−**30** (added with relevant spectroscopic characterization, ^{1}H- and ^{13}C NMR spectra). This material is available free of charge via the Internet at http://pubs.acs.org.

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