Pergamon

Tetrahedron Letters 40 (1999) 7043–7046

TETRAHEDRON LETTERS

Preparation of Formate Esters from *O*-TBDMS/*O*-TES Protected Alcohols. A One-Step Conversion Using the Vilsmeier-Haack Complex $POCl_3$/DMF

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Received 30 June 1999; accepted 27 July 1999

Abstract: *O-tert*-Butyldimethylsilylated (*O*-TBDMS) or *O*-triethylsilylated (*O*-TES) alcohols were converted in one step to their corresponding formates under Vilsmeier-Haack conditions ($POCl_3$/DMF). The scope and limitations of this novel reaction for interconverting alcohol protecting groups are described.

Keywords: Formylation / Vilsmeier-Haack reaction / Protecting groups / Formates

O-Formylation of alcohols is one of the most useful and versatile reactions in protective organic chemistry. Numerous formylating reagents have thus been developed, each with its particular advantages or limitations.[1] As a result of the rather harsh experimental conditions, such as medium acidity, formylation temperatures and/or accompanying side reactions (halogenations or dehydrations), case by case optimization is required, especially for sensitive or polyfunctional substrates.[2]

Our exploratory work towards synthesis of glycal-based peptidomimetics led us to discover a quite unusual and general *one-step conversion of O-tert-butyldimethylsilyl or O-triethylsilyl alcohols to formates* (R-OSiR'$_3$ → R-OCHO) by means of the Vilsmeier-Haack complex $POCl_3$/DMF.[3] Such an exchange of alcohol protecting groups without any intermediate deprotection is of great interest in multi-step syntheses. Only very few reactions of this type have been reported previously, such as the conversion: of allyloxycarbonyl derivatives of alcohols to allyl ethers (2 % $Pd(PPh_3)_4/PPh_3$, benzene);[4] of methyl/methylthiomethyl ethers to acetates ($TMSCl/Ac_2O$);[5] of tetrahydropyranyl/silyl ethers to acetates or pivaloates (cat. $ZnCl_2$/R"COCl, CH_3CN);[6] of *tert*-butyl and *tert*-amyl ethers to acetates (cat. $FeCl_3/Ac_2O$, ethereal solvant)[7-9] or *tert*-butyldimethylsilyl ethers (TBDMSOTf/2,6-lutidine, CH_2Cl_2);[10] of tetrahydropyranyl ethers to *tert*-butyldimethylsilyl ethers (TBSOTf, CH_2Cl_2);[11] of MEM ethers to MOM ethers (Me_2BBr, CH_2Cl_2);[12,13] or of benzyl ethers to the corresponding acetates (cat. $SnBr_2$, AcBr, CH_2Cl_2).[14]

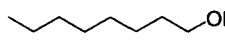
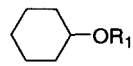
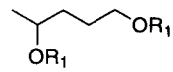
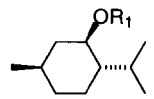
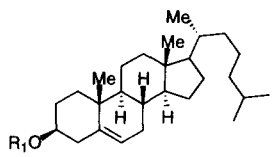
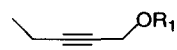
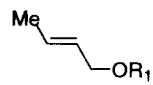
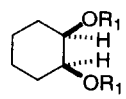
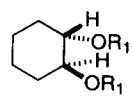
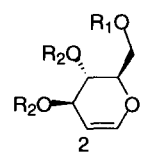
To the best of our knowledge, there is only one report of the conversion of the primary *n*-cetyl-OTBDMS to the corresponding formate *n*-cetyl-OCHO by means of PPh_3/CBr_4 in $HCOOEt/H_2O$.[15] Since this transformation is catalyzed by *in situ* generated HBr (pH medium at reaction completion ~ 1-2), it would not be applicable to acid-sensitive substrates.

This letter describes our recent results demonstrating that the Vilsmeier-Haack complex $POCl_3$/DMF has potential for such a one-step conversion. In order to explore its scope and limits, suitable *O-tert*-butyldimethyl-

0040-4039/99/$ - see front matter
PII: S0040-4039(99)01453-7

silyl or *O*-triethylsilyl alcohols where selected and prepared by means of Hanessian's protocol (Table, all entries, yield range: 89-98 %).

Table: One-step conversion of *O*-silylated alcohols to the corresponding formates

Entry	*O*-Silylated alcohol (a)		Formate[Yield (%); Time (d)]
1		**1a**: R_1 = TBDMS	**1c**: R_1 = CHO (91, 4 h)
2		**2a**: R_1 = TBDMS	**2c**: R_1 = CHO (98, 5 h)
3		**3a**: R_1 = TBDMS	**3c**: R_1 = CHO (60, 5 h)
4		**4a**: R_1 = TBDMS	**4c**: R_1 = CHO (78, 14 h)
5		**5a**: R_1 = TBDMS	**5c**: R_1 = CHO (88, 3 h)
6		**6a**: R_1 = TBDMS	**6c**: R_1 = CHO (62, 5 h) (b)
7		**7a**: R_1 = TBDMS	**7c**: R_1 = CHO (69, 4 h) (b)
8		**8a**: R_1 = TBDMS	**8c**: R_1 = CHO (74, 14 h)
		8b: R_1 = TES	**8c**: R_1 = CHO (79, 14 h)
9		**9a**: R_1 = TBDMS	**9c**: R_1 = CHO (71, 14 h)
		9b: R_1 = TES	**9c**: R_1 = CHO (98, 14 h)
10		**10a**: $R_1 = R_2$ = TBDMS	**10c**: R_1 = CHO, R_2 = TBDMS [70, 8 h (b); 80, 72 h (c)]

(a) Chlorosilane reagent (1.2 molar equiv./OH function), imidazole (2.5 molar equivalent/OH function), dry DMF, room temperature, 1-5 h
(b) $POCl_3$ (1.1 molar equiv./silyl function), dry DMF, 0 °C
(c) The medium is added with anhydrous pyridine (3.3 equiv./$POCl_3$)
(d) Time of reaction completion (TLC)

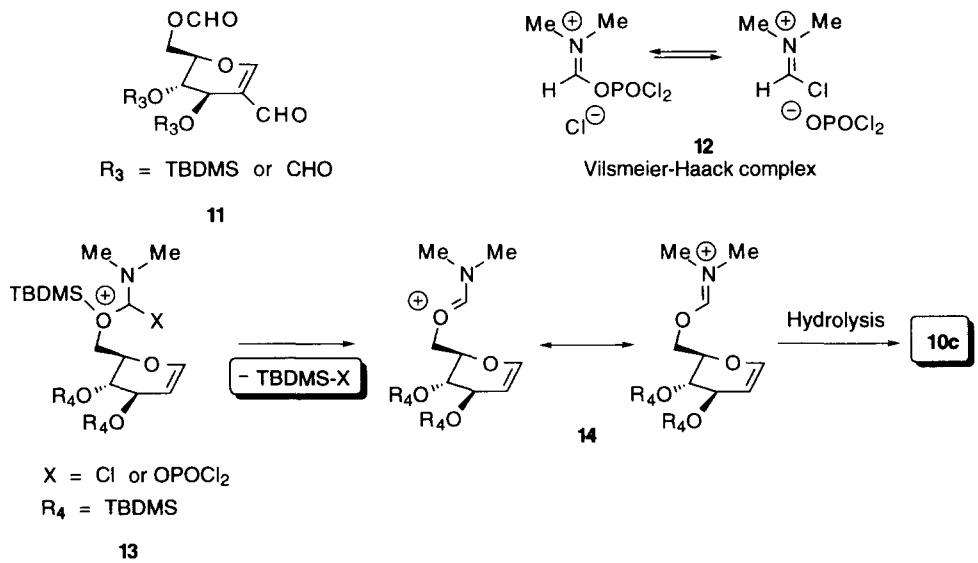
Structural variations include degree of substitution (primary *versus* secondary alcohols), chemical type (aliphatic, allylic or propargylic alcohols) and multifunctionality (1,2-/1,4-diols and D-glucal derived polyols).

A typical procedure: A stirred cold DMF solution of the complex $POCl_3$/DMF (1.65 mmol, 1.0 mL anhydrous DMF, 0 °C) was added slowly with the appropriate silylated alcohol (1.5 mmol, 2.0 mL DMF) under nitrogen. After the mixture has been agitated at 20 °C till completion of the reaction (TLC, see the reaction times in the Table), the medium was hydrolyzed at 0 °C with a saturated $NaHCO_3$ aqueous solution (30 mL). After the usual work-up, the crude formate was purified by flash chromatography on a silica gel column and characterized spectroscopically.

From the results given in the Table, some interesting comments can be made:

1. Irrespective of the silylated alcohol or silyl group (*O*-TBDMS/*O*-TES), the yields of formates **1c-10c** were consistently in the medium- to high-yield range (60-98 %); in practise, the yields were limited in fact by the intrinsic volatilities of **3c**, **6c** and **7c** (entries 3, 6, 7).
2. In addition to silylated aliphatic alcohols or diols **1a-5a** and **8a-10a** (entries 1-5, 8-10), propargylic and *E*-ethylenic functions were well tolerated (entries 6 and 7, **6c**: 62 %, **7c**: 69 %, ^{1}H-NMR (200 MHz, $CDCl_3$): J_{H2H3} = 15.0 Hz).
3. The reaction of *cis- or trans-1,2-cyclohexanediols* with the Vilsmeier complex PhCOCl/DMF is known to afford solely the respective *cis-/trans*-monoformates.[16] In contrast, the silylated precursors *cis*-**8a/8b** or *trans*-**9a/9b** produced the expected diformates *cis*-**8c** (74/79 %, entry 8) and *trans*-**9c** (71/98 %, entry 9) (^{1}H-NMR (200 MHz, $CDCl_3$) *cis*-**8c**: δ = 5.16-5.18 ppm, doublet, $H_1 + H_2$; *trans*-**9c**, δ = 4.92-5.00 ppm, multiplet; $H_1 + H_2$). Interestingly, neither the silyl groups nor the *cis-/trans*-relationship relative to those precursors had an influence on the outcome of the formylation.
4. It is worthwhile to note the extreme selectivity of formylation of **10a** (1.5 mmol, $POCl_3$/DMF complex: 4.95 mmol, 9 mL DMF) to **10c**; only the primary *O*-TBDMS function was modified, and not the secondary functions (70 %, entry 10). In that particular case, there was neither subsequent *O*-formylation to di-/tri-formates nor *C(2)*-electrophilic formylation to afford any conjugated enal of type **11**, as expected from the literature data.[17]

Scheme



In terms of the mechanism (Scheme), the Vilsmeier-Haack complex **12** (equilibrium mixture of the depicted salts) [3] adds the silylated glucal **10a** to form the cation **13**. TBDMS-X is eliminated, giving the cationic species **14** (formation of the thermodynamically strong Si-Cl/Si-O bond, 111.0 and 128.2 kcal/mmol respectively). Consequently, the unreacted complex **12** cannot *C*-formylate the cyclic enol ether of the electronically deficient cations **13** and/or **14**. It is not clear how this deactivation would affect the nucleophilicity of the remaining C(3)/ C(4) *O*-silylated hydroxyls of **13/14** or whether the observed selectivity of **12** indeed be a pure effect of steric hindrance (multifunctionality effect). The subsequent hydrolysis of the imidate **14** produces the corresponding formate.

5. Considering the acid sensitivity of **10a**, adding anhydrous pyridine retarded the conversion to **10c** (72 h, 3.3 equiv. Py/$POCl_3$) but improved the yield (80 %, entry 10).

6. Retention of the configuration for **4c**, **5c**, **8c** and **9c** seemed likely, on the basis of the above-described mechanism.[3,16,18,19] In addition, deformylation of **4c** and **5c** led to the same starting (-)-menthol and 3β-cholesterol respective precursors of **4a** and **5a** (CH_3OH-concentrated NH_4OH, 14 h, 75 and 80 % unoptimized yields, TLC and NMR checking).

In conclusion, the overall applicability, the mildness of the reaction conditions and the use of common reagents provide a convenient methodology to convert *O*-TBDMS/*O*-TES alcohols into their corresponding formates in one step. Further extensions of this novel conversion are presently under investigation.[20]

Acknowledgement: This work has been generously supported by the Institute for Applied Biosciences (internal granting and a post-doctorate fellowship to S. K. (Ben-Gurion University of the Negev). J.-P. Lellouche wishes to aknowledge the Rachi Foundation for its financial support through the obtention of a Guastalla fellowship.

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