Vilsmeier–Haack Reagents. Novel Electrophiles for the One-Step Formylation of *O*-Silylated Ethers to *O*-Formates

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Received 30 October 2003

new tools

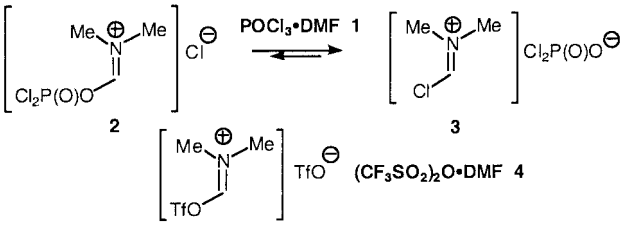
Abstract: Various *O*-silylated substrates were effectively converted in one-step to their corresponding *O*-formates using electrophilic racemic and homochiral Vilsmeier–Haack reagents. Reactivity trends of these transformations were examined that, specifically, emphasized their synthetic potential.

Key words: Vilsmeier–Haack complexes, deprotection of *O*-silyl ethers, one-step deprotection, preparation of *O*-formates, formyl glycosides

Introduction

Synthetic planning toward complex multifunctional organic compounds emphasize the importance of a judicious choice of specific protective groups (Pgs).[1,2] Their careful selection, their introduction, and cleavage conditions are essential milestones critical for success. Not astonishingly, current trends in the field are aimed at the discovery of new Pgs or milder cleavage conditions. In this regard, organic chemists devote much attention to synthetic transformations that allowed Pg exchanges without isolating deprotected intermediates. Such one-step Pg interconversions should result in higher overall yields, should bypass problematic intermediate deprotections, and should minimize waste during multi-step synthesis. In this context, *O*-silyl ethers R-OSiR′$_3$ have proved very popular as OH-protecting groups since (i) they are easily introduced in high-yields, (ii) present modulatory chemical stabilities over a wide range of conditions, and (iii) can be deprotected by fluoride-based, acidic/basic or strongly reducing/oxidizing reagents. Nevertheless, their deprotections can be very often problematic for sensitive multi-functional substrates,[3,4] so alternate orthogonal milder cleavage conditions involving Pg exchanges could be of major interest. Prior to our work, few one-step transformations of *O*-silyl ethers to acetates[5] or benzyl/methyl,[6] and THP ethers[7] were known. Synthetic limitations were clearly encountered due to harsh reaction conditions (strong Lewis acids, in situ generated basic alkoxides, high temperatures).

This ‘New Tool’ article will survey our most recent findings dealing with the one-step conversion of *O*-silyl ethers to their corresponding *O*-formates R-OSiR′$_3$ → R-OCHO mediated by electrophilic Vilsmeier–Haack (VH) reagents. *O*-Formates can be removed in very mild conditions (0.6 M NH_4OH in MeOH, 20 °C) without affecting sterically more hindered *O*-acetates, as well as hydrolytically sensitive *O*-silyl ethers.[1,2] Typically, VH-reagents **1** (equilibrium mixture of the two salts **2** and **3**) and **4** were found effective for such Pg interconversions (Scheme 1). VH reagents are electrophilic species that are able to formylate nucleophilic substrates such as activated aromatics, double bonds, enolizable ketones, or amines.[8,9] They have also found extensive use in halogenating and dehydrating processes. Practically, these electrophiles can be easily prepared by reaction of an inorganic acid halide or anhydride [e.g. $POCl_3$, $SOCl_2$, $COCl_2$, or $(CF_3SO_2)_2O$] with a *N*,*N*-disubstituted formylamide such as DMF at 0–20 °C.



Scheme 1 VH-Reagents **1** and **4**

O-TES and *O*-TBDMS Silylated Ethers

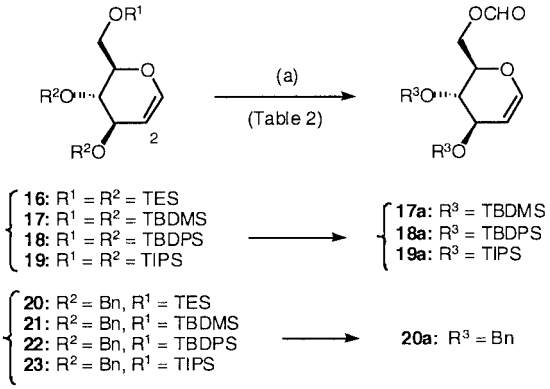
Early exploratory works dealt with reactivity studies of various *O*-TES and *O*-TBDMS silyl ethers that were reacted with the prototypical VH-reagent **1** prepared from $POCl_3$ (Table 1, see also the Typical Experimental Procedure).[10] Substrates presenting different degrees of substitution (primary versus secondary ethers), chemical type (aliphatic, neopentyl, allylic, and propargylic ethers), and multifunctionality (1,2-/1,4-diol ethers) were examined. The formation of the corresponding *O*-formates by Pg exchange appeared very clean based on TLC and ^{1}H-NMR checking. Conversion yields were consistently in the medium to the high range (60–98 %) although limited by the volatility of formates **7**–**10** (Table 1, entries 3–6). Propargylic and *E*-ethylenic functions were well tolerated in these conditions (entries 3,4) while *cis/trans*-diastereoselectivities in 1,2-cyclohexane-di-*O*-formates **12**/**13** and **14**/**15** were retained when compared to the starting *O*-silylated diols (entries 8,9). Retention of configuration for

SYNLETT 2004, No. 3, pp 0564–0571
Advanced online publication: 26.01.2004
DOI: 10.1055/s-2004-815435; Art ID: T02003ST

substrates **10** and **11** has been observed, which is compatible with the proposed formylation mechanism (Scheme 3).[10]

O-Silylated D-Glucal Derivatives

The scope and limitations of the above Pg interconversion mediated by the VH-reagent **1** needed further investigation, mainly considering multifunctional *O*-silyl ethers.[11] *O*-Silylated D-glucal-based precursors **16**–**19**[11] (Scheme 2) with various degrees of steric hindrance at the silicon were tested not only with reagent **1**, but also with the known more electrophilic VH-reagent **4** (prepared from triflic anhydride Tf_2O and DMF).[12] These sugar-derived cyclic enol ethers are acid-sensitive, contain a dense array of *O*-silyl ethers of primary, secondary allylic nature in a 1,2/1,3/1,4-relationships that should provide different reactivities. The intracyclic enol ether itself could be competitively C-formylated by reagents **1** and **4** at position C2 to afford *C2*-formylated glucal derivatives. For example, the tri-*O*-benzyl-D-glucal is known to react in this way with reagent **1**.[13]



Scheme 2 (a) $POCl_3$·DMF **1** or $(CF_3SO_2)_2O$·DMF **4**, anhyd DMF, 0–20 °C

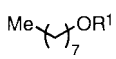
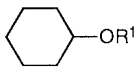
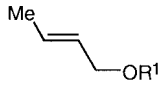
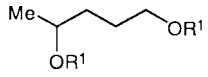
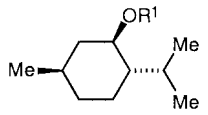
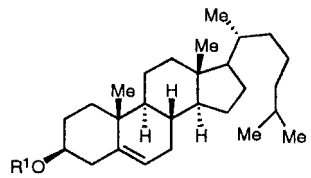
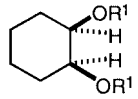
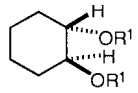
Relative to these D-glucal-based precursors, reagent **1** and the Tf_2O-based reagent **4** were found able to formylate substrates **17**, **18**, and **20**–**23** affording the corresponding *primary C6-O*-formates **17a**, **18a**, and **20a** in medium to high yield (50–91%, Table 2). Globally, reagent **4** was found to be more reactive and more efficient than reagent **1** resulting in shorter reaction times. As rationalized later (Scheme 3), no competitive C2-formylation products

Biographical Sketches

Jean-Paul Lellouche was born in Constantine (Algeria) in 1955. He received his diploma of Engineer in Organic Chemistry from the ESCIL (Ecole Supérieure de Chimie Industrielle de Lyon, Claude Bernard University, Lyon, France) in 1978. Thereafter, he joined the CEA (Commissariat à l'Energie Atomique, Gif-sur-Yvette, France) to earn his PhD degree in 1981 under the direction of Dr. Louis Pichat (multi-step syntheses of ^{14}C-/^{3}H-labeled organic molecules). In 1997, he moved to Negev, the Institute for Applied Biosciences at the Ben-Gurion University (Beer-Sheva, Israel) as an Associate-Professor in Organic Chemistry, where he received a Guastella fellowship from the Rashi Foundation. He subsequently joined the Department of Chemistry at the Bar-Ilan University in October 2000. He is currently developing novel pyrrole-/carbazole-based conducting polymers and related nanosized composites for diverse bio- and immunosensing applications. His additional main scientific contributions deal with asymmetric synthesis using homochiral η^4-dienyl tricarbonyliron(0) complexes and related cations toward biologically active di-HETEs, sulfido-leukotrienes, and phospholipids. He has authored 68 papers, 5 patents and 2 book chapters in organometallic and fluorine chemistries (see the following URL: http://www.biu.ac.il/ESC/ch/faculty/lellouche/jplellint.html).

Vadim Kotlyar was born in Ekaterinenburg, Russia in 1974. He received his BSc and MSc degrees in Pharmaceutical Chemistry from the Bar-Ilan University (Ramat-Gan, Israel) in 1996 and 1998, respectively. He performed his military service at the Institute of Clinical Toxicology and Pharmacology at the Chaim Sheba Medical Center (Tel-Hashomer, Israel) as an analytical chemist from 1997–2000. After which, he moved to the Department of Chemistry of the Bar-Ilan University working with Professor Jean-Paul Lellouche to complete his PhD studies. He is currently working on the development of selective asymmetric one-step conversions of *O*-silyl ethers to their corresponding *O*-formates. His research interests are in the areas of high-throughput experimentation and asymmetric synthesis.

Table 1 Formylation of *O*-TES and *O*-TBDMS Silylated Ethers Mediated by the VH-Reagent **1**

Entry	*O*-Silylated Ether	*O*-Formate[c]	Yield (%)	Time (h)
1	 **5**[a]	**5a**	91	4
2	 **6**[a]	**6a**	98	5
3	 **7**[a]	**7a**	62	5
4	 **8**[a]	**8a**	69	4
5	 **9**[a]	**9a**	60	5
6	 **10**[a]	**10a**	78	14
7	 **11**[a]	**11a**	88	3
8	 **12**[b]	**12a**	79	14
	13[a]	**12a**	74	14
9	 **14**[b]	**14a**	98	14
	15[a]	**14a**	71	14

[a] R^1 = TBDMS.
[b] R^1 = TES.
[c] R^1 = CHO.

were ever isolated during these trials. Whatever reagent, anhydrous pyridine was found to be compatible with the transformation. In this case, conversion yields were slightly increased at the expense of reaction times (entries 1 and 2). This last result is particularly important regarding acid-sensitive substrates. The silyl groups in **20**–**23** could be graded by their decreasing O(6)-formylation reactivity toward **1** and **4** as follows: **1**: TES >> TBDMS >> TIPS >> TBDPS and **4**: TES >> TBDMS >> TBDPS ca. TIPS. As expected, this reactivity scale follows increasing steric hindrance at the silicon.

Nevertheless, some limitations have been already identified. For example, the tri-*O*-TES-D-glucal **16** was rapidly destroyed (30 min reaction, results not shown in Table 2) even in the presence of pyridine, while the dibenzylated mono-*O*-TES-D-glucal **20** has been successfully formylated by reagents **1** and **4** (entry 5, 70% and 84%). A sterically hindered *O*-TIPS group could be formylated but the formylation outcome depended on substrates. Compared to the unreactive *per*-*O*-TIPS precursor **19**, the less encumbered and/or more electronically activated di-*O*-benzyl-D-glucal **23** was successfully C(6)-O-formylated (entries 4 and 8, 10 versus 85% and 91%).

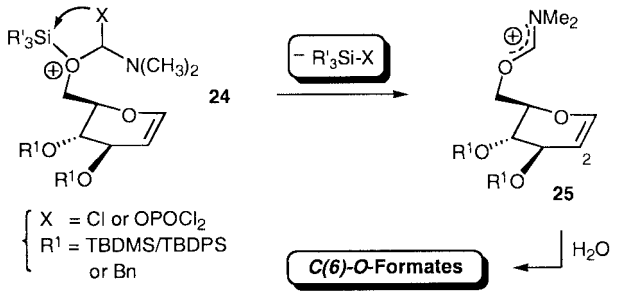
Table 2 Selective O-Formylation of *O*-Silylated D-Glucal Derivatives

Entry	Precursor	Product (R^3)	**1**		**4**	
			Yield (%)	Time (h)	Yield (%)	Time (h)
1	**17**	**17a** (TBDMS)	70	8	69	6
2	**17**	**17a** (TBDMS)	80[a]	72	78[a]	48
3	**18**	**18a** (TBDPS)	50	8	65	8
4	**19**	**19a** (TIPS)	10	48	10	48
5	**20**	**20a** (Bn)	70	3	84	2
6	**21**	"	82	4.5	85	3.5
7	**22**	"	60	24	70	8
8	**23**	"	85	8	91	8

[a] Anhyd pyridine was added (3.3 equiv/$POCl_3$).

Conversion Mechanism

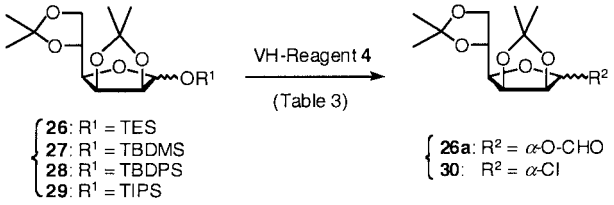
A likely mechanism for these conversions has been exemplified for D-glucal-based precursors (Scheme 3). The first is conversion of the sterically-driven electrophilic addition of VH-reagents **1** and **4** to the primary *O*-silyl ether function affording intermediate oxonium cations of type **24**. Favored by the formation of the thermodynamically strong Si–Cl/Si–O bonds (111.0 and 128.2 kcal, respectively),[14] the β-elimination of the R'_3Si-X species affords a positively charged *C(6)*-located imidate **25** that, electronically deactivates additional O–Si bonds to react similarly. This explains why a three/five-fold excess of reagents **1** or **4** did not result in the isolation of some accompanying di/tri-formylated products (results not shown in Table 2).[15,16] Smooth hydrolysis of imidates of type **25** produces the corresponding *C(6)*-*O*-formates.



Scheme 3 Imidate-related conversion mechanism

1-*O*-Silylated D-Mannofuranose Derivatives

Reagents **1** and **4** were further tested on 1-*O*-silylated D-mannofuranose derivatives **26**–**29**. Corresponding 1-*O*-formates should be produced via intermediate anomeric imidates (Scheme 4 and Table 3).[17] The rationale that supported these trials was to test the mild generation of positively charged anomeric imidates without any anomeric activation by heavy toxic metals or strong Lewis acids. Such transformations should be potentially useful for the development of a general glycosidation protocol of thermodynamically stable 1-*O*-silylated donors, that should be mediated by Vilsmeier–Haack reagents.



Scheme 4 Reaction of 1-*O*-silylated D-mannofuranose derivatives **26**–**29** with VH-reagents **1** and **4**

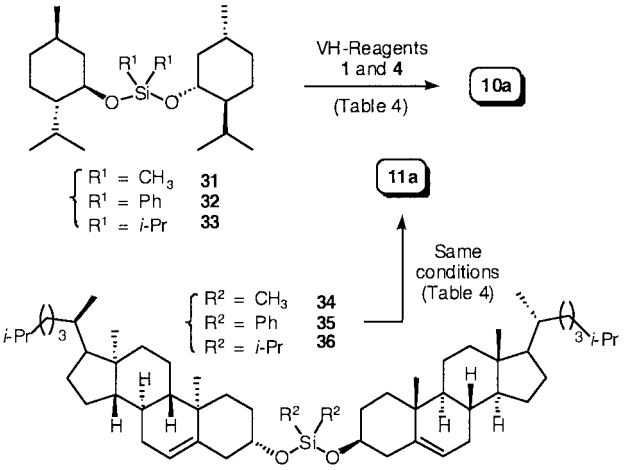
Basically, reagents **1** and **4** were found to react quite differently with 1-*O*-silylated precursors **26**–**29** that possessed increasing steric requirements at silicon. Reagent **1** reacted with **26** (α/β = 55:45, 3 h) and **27** (α/β = 95:5, 14 h) to afford the chromatographically labile α-chloride **30** (65–75 %). Most likely, anomeric oxonium or imidates species could be substituted by nucleophilic chloride anions generated in the medium. On the contrary, reagent **4**, *that possesses a non-nucleophilic triflate counter-anion*, lead to the expected α-formate **26a** in yields depending on the silyl group hindrance and on the number of VH-reagent equivalents (Table 3, entries 1 and 2, 2 and 14 h reaction time, 94% and 85%). Whatever conditions, the 1-*O*-TBDPS and 1-*O*-TIPS derivatives **28** and **29** were found to be too hindered to react efficiently (entries 3 and 4, conversion yields less than 28 %, 14 h reaction time).

Table 3 *O*-Formylation of Anomeric *O*-Silylated D-Mannofuranose Derivatives Mediated by the VH-Reagent **4** (yields reported for **26a**)

Entry	Precursor (R^1)	**4** (1.0 equiv)	**4** (2.0 equiv)	**4** (4.0 equiv)
1	**26** (TES)	55	94	–
2	**27** (TBDMS)	26	54	85
3	**28** (TBDPS)	5	10	28
4	**29** (TIPS)	< 5	10	15

C2-Symmetrical Dialkoxysilanes $R^1O\text{-}Si(R^2)_2\text{-}OR^1$

Intramolecular reactions involving species pre-organized by linkage to a removable 'temporary silicon connection' have been recently developed to predictably enhance attachment regio- and stereoselectively.[18] Intramolecular glycosidations, [4+2]-Diels–Alder condensations, ring-closure metatheses, ene-ene/ene-yne [2+2]- and [3+2]-nitrone cycloadditions typically resulted in cyclic *O*-silylated dialkoxysilanes. Following condensation, the silicon tether needed to be eliminated to liberate OH-containing reaction products. This overall concept of 'reacting pre-organized species' would be synthetically much more attractive if a non-fluoride-based deprotective protocol could be made available to liberate *O*-protected rather than OH-products. Consequently, we examined the reactivity of reagents **1** and **4** with model *C2*-symmetrical dialkoxysilanes $R^1O\text{-}Si(R^2)_2\text{-}OR^1$ **31**–**36**, that were easily accessible from (–)-menthol and 3β-cholesterol respectively (Scheme 5 and Table 4).[19]



Scheme 5 Reaction of VH-reagents **1** and **4** with *C2*-symmetrical di-alkoxysilanes

Whatever the conditions, reagent **1** was always found to be the most efficient affording formates **10a** and **11a** in a medium to good yield (46–83 %). Except for the less hindered methyl-substituted dialkoxysilane **34** (R^2 = Me, entry 10), the more electrophilic triflate-based reagent **4** invariably afforded low to average conversion yields (20–68 %). This last result did not follow the usual efficiency trend that characterized the O-formylation of simple *O*-silylated ethers. Some other valuable features should be noticed regarding reagent **1**. Except for one entry (entry 9), conversion yields were similar for the two reagent/sub-

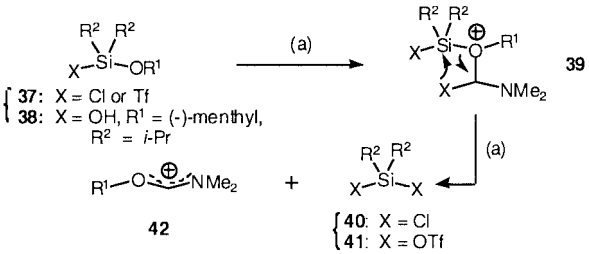
Table 4 One-Step O-Formylation of *C2*-Symmetrical Dialkoxysilanes Mediated by VH-Reagents **1** and **4**

Entry	Precursor (1.0 equiv)	**1** or **4** (equiv)	*O*-Formate **10a**		*O*-Formate **11a**	
			1 (%)	**4** (%)	**1** (%)	**4** (%)
1	**31**	1.0	73	20	–	–
2	**32**	"	80	30	–	–
3	**33**	"	80	36	–	–
4	**31**	2.0	82	68	–	–
5	**32**	"	77	56	–	–
6	**33**	"	82	66	–	–
7	**34**	1.0	–	–	82	50
8	**35**	"	–	–	75	50
9	**36**	"	–	–	46	30
10	**34**	2.0	–	–	75	78
11	**35**	"	–	–	76	59
12	**36**	"	–	–	83	5

[a] Reagents **1** and **4** have been reacted with *C2*-symmetrical dialkoxysilanes **31**–**36** in anhydrous DMF (–5 °C to r.t., 18 h) using the indicated molar ratios between VH-reagents and substrates

strate ratios of 1.0 and 2.0 (entries 1–3 versus 4–6 and entries 7 and 8 versus 10–12). Most likely, another reagent **1**-like compound has been generated that possessed similar O-formylating capabilities. Remarkably, conversions were found to be independent of increasing steric hindrance at silicon (R^2 varying from Me to *i*-Pr).

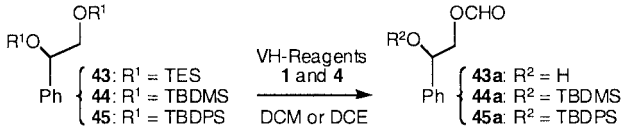
Based on our former mechanism (Scheme 3), the overall difference of reactivity observed between reagents **1** and **4** can be rationalized in the following simple way (Scheme 6). The electrophilic addition of reagents **1** or **4** (1 equiv) to the first O–Si bond of dialkoxysilanes substrates **31**–**36** should afford the imidate **42** (1 equiv) in addition to the neutral species **37** (X = Cl or Tf). The second O–Si bond of this last silylated intermediate **37** can react similarly, affording a second equivalent of **42** accompanied by the dichlorosilane **40** or by the bistriflated silane **41**. The critical step **37** → **39** should be clearly disfavored when considering a less nucleophilic intermediate **37** (X = OTf) versus **37** (X = Cl). Supporting this stepwise mechanism, the chromatographically labile silanol ether **38** resulting from the hydrolysis of **37** (entry 6) has been isolated and partially characterized by spectroscopic and analytical means [high-field ^{1}H NMR, 300 MHz, $CDCl_3$ and EI-MS/DCI-MS (NH_3 and CH_4)].



Scheme 6 (a) VH-reagents **1** or **4**, anhyd DMF, 0–20 °C

Improved Solvent-Dependant One-Step O-Formylations. CH_2Cl_2/DCE- versus DMF-Based Protocols

Experiments described up to now employed DMF not only as the *N*-formyl dialkylamine precursor of VH-reagents **1** and **4**, but also as the conversion solvent *(DMF-based protocol)*. In a further step, various solvents ranging from aprotic non-polar to polar were screened to find suitable candidates that should be compatible with one-step O-formylations mediated by VH-reagents **1** and **4** (data not shown). Similar conversions could be more efficiently performed in anhydrous dichloromethane (*CH_2Cl_2-based protocol*) or 1,2-dichloroethane (*DCE-based protocol*), *where DMF acted uniquely as a reagent.* For comparison, best results of O-formylations using the DMF-based protocol on the various O-silylated substrates **17**–**19** (Scheme 2), **32**, **33** (Scheme 5) and **43**–**45** (Scheme 7) were gathered in Table 5 (5th column). In parallel, the same series of substrates was reacted using modified



Scheme 7 Reactivity of VH-reagents **1** and **4** in CH_2Cl_2 or DCE

CH_2Cl_2/DCE-based protocols (6th column, see also the Improved CH_2Cl_2/DCE-Based Experimental Procedure).

Depending on substrates, CH_2Cl_2- or DCE-based O-formylations were generally found to be higher yielding (Table 5, 71–98%) than DMF-based ones (10–82%). For example, the strongly hindered *per*-*O*-TIPS D-glucal derivative **19** could not be formylated easily by reagents **1** and **4** in DMF (conversion yields less than 10%, entry 5). On the contrary, the DCE-based protocol afforded the corresponding primary *C(6)*-*O*-formate **19a** in quite a high 86% yield (entry 6). Similar reactivity trends were observed with the two *O*-TBDMS and *O*-TIPS glycols **44** and **45** toward primary *O*-formates **44a** and **45a** (entries 11 versus 12: 63% versus 90% yield, entry 13: 10% versus 71% yield). Again since useful for acid-sensitive substrates, pyridine was found to be compatible with transformations operated in CH_2Cl_2/DCE (entries 1–4). Better conversion yields for substrates **17** and **18** have been observed (entries 1,2: 80% versus 89% in a shorter reaction time: 72 h versus 14 h; entries 3,4: 65% versus 78%).

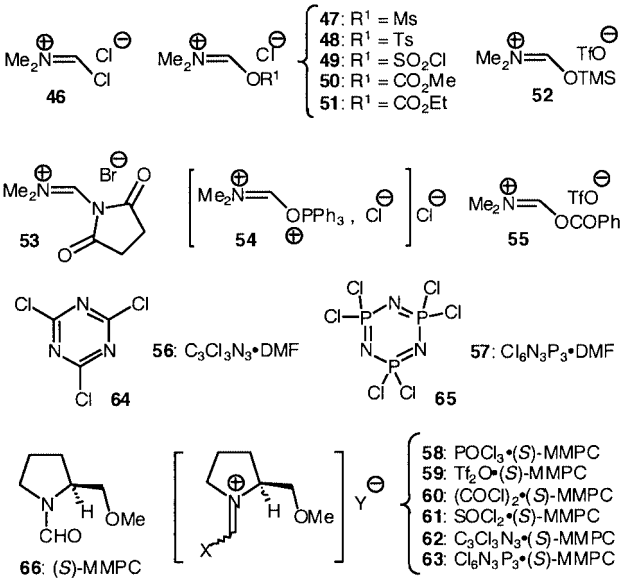
Table 5 O-Formylations in CH_2Cl_2 or DCE. Comparison with the Standard DMF-Based Protocol

Entry	Substrate	Product	Time (h)	**1** and/or **4** DMF (%)[a]	**1** and/or **4** Solvent (%)[b]
1	**17**	**17a**	72	**1** (80)[c]	–
2	"	"	14	–	**4**: DCE (89)[c]
3	**18**	**18a**	"	**4** (65)	–
4	"	"	72	–	**4**: CH_2Cl_2 (78)[c]
5	**19**	**19a**	48	**1** and **4** (10)	–
6	"	"	14	–	**1**: DCE (86)
7	**32**	**10a**	"	**1** (77)	**1**: CH_2Cl_2 (98)
8	**33**	"	"	**1** (82)	**1**: CH_2Cl_2 (98)
9	**43**	**43a**	"	**1** (61)[c]	–
10	"	"	"	–	**1**: DCE (81)
11	**44**	**44a**	"	**1** (63)	–
12	"	"	4	–	**1**: DCE (90)
13	**45**	**45a**	14	**1** and **4** (10)	**4**: DCE (71)

[a] Results obtained with the DMF-based protocol.
[b] Results obtained with the CH_2Cl_2/DCE-based protocols.
[c] Anhyd pyridine was added.

Novel Racemic and Homochiral VH-Reagents

Interestingly, the two *N*-formyl dialkylamine and inorganic acid halide/anhydride components can be systematically changed to introduce molecular diversity. On the one hand, novel electrophilic VH-reagents, different from the former reagents **1** and **4**, could be synthesized and screened regarding their O-formylation capabilities. On the other hand, CH_2Cl_2/DCE-based O-formylations are even more attractive synthetically, since homochiral *N*-formyl amines could afford novel homochiral VH-reagents. These optically active VH-reagents should pave the way to innovative kinetic resolutions or deracemizations of racemic *O*-silylated substrates.



Scheme 8 Novel racemic and homochiral VH reagents **46**–**63**

Fulfilling the above first step, recent results from our laboratory demonstrated unambiguously that additional racemic and homochiral VH-reagents could perform similar O-formylations in DMF or DCE (Scheme 8 and Table 6). New racemic VH-reagents that were included in this preliminary study were: $(COCl)_2$·DMF (**46**),[20] MsCl·DMF (**47**),[21] TsCl·DMF (**48**),[21] SO_2Cl_2·DMF (**49**),[8,9] $ClCO_2Me$·DMF (**50**),[8,9] $ClCO_2Et$·DMF (**51**),[8,9] TMSOTf·DMF (**52**),[22] NBS-PPh_3·DMF (**53**),[23] [Cl_2·PPh_3]·DMF (**54**),[24] [PhCOCl–AgOTf]·DMF (**55**),[25] and, finally, the last two $C_3Cl_3N_3$·DMF (**56**) and $Cl_6N_3P_3$·DMF (**57**), formed by reaction of cyanuric chloride ($C_3Cl_3P_3$, **64**) and 2,4,6-trichloro[1,3,5]triazine ($Cl_6N_3P_3$, **65**) respectively with DMF.[26] The novel homochiral VH-reagents **58**–**63** [X and Y = Cl, $Cl_2P(O)O$, OTf, *O*-heterocycle] were similarly prepared in DCE by reaction of $POCl_3$, Tf_2O, $(COCl)_2$, $SOCl_2$, $C_3Cl_3N_3$ (**64**) and $Cl_6N_3P_3$ (**65**) with the commercially available homochiral *N*-formyl amine (*S*)-2-methoxymethyl-pyrrolidine-1-carbaldehyde (**66**) [(*S*)-MMPC, Aldrich, ee ≥ 99 %].

The O-formylation capabilities of these novel VH-reagents were screened using the test O-formylation of the neopentyl *rac*-*O*-TES menthol *rac*-**10** → *rac*-**10a** (Table 1, entry 6). VH-reagents and solvent conditions that provided *a quantitative conversion* (yields in *rac*-**10a** better than 95 %) were identified and gathered in Table 6. Interestingly, 7 new racemic (entries 1–7) and 4 homochiral VH-reagents (entries 8–11) have been found to be effective, emphasizing the generality and the synthetic potential of such one-step O-formylations.

Table 6 O-Formylation of *rac*-*O*-TES Menthol. Reactivity Screening Using Racemic and Homochiral VH Reagents **46**–**63**

Entry	VH-Reagent		Solvent
1	$(COCl)_2$·DMF	**46**	DMF and DCE
2	MsCl·DMF	**47**	DMF
3	TsCl·DMF	**48**	"
4	SO_2Cl_2·DMF	**49**	DCE
5	[PhCOCl-AgOTf] ·DMF	**55**	DMF and DCE
6	$C_3Cl_3P_3$·DMF	**56**	"
7	$Cl_6N_3P_3$·DMF	**57**	"
8	$POCl_3$·(*S*)-MMPC	**58**	DCE
9	$(COCl)_2$·(*S*)-MMPC	**60**	"
10	SO_2Cl_2·(*S*)-MMPC	**61**	"
11	$Cl_6N_3P_3$·(*S*)-MMPC	**63**	"

Conclusions and Outlook

One-step O-formylations of diverse *O*-silylated substrates have been mediated by electrophilic Vilsmeier–Haack reagents. These Pg interconversions have been found to be general and synthetically efficient. Minimizing steps and waste, they should provide a very stimulating entry to alternative, more effective protective-deprotective strategies useful in multi-step synthesis. On-going progress, that should broaden their synthetic potential, will involve the development of novel glycosidation reactions using stable 1-*O*-silylated donors, and of new solid phase-supported VH-reagents for *O*-silylated ether scavenging (scavenging polymer-supported VH-reagents). In parallel, O-formylations mediated by homochiral VH-reagents are currently developed targeting the kinetic resolution of secondary/tertiary *O*-silylated ethers and the deracemization of various *meso O*-silylated substrates. These works will be reported in due time.

Formylation; General Procedure

$POCl_3$ (1.1 equiv per O–Si bond to be potentially formylated) is dissolved in anhyd DMF (3 mL) under nitrogen, cooled to 0 °C, agitated for 30 min at the same temperature and added dropwise to a cold solution of the *O*-silylated substrate (1.0 mmol, 2 mL of anhyd DMF, 0 °C). The medium is then stirred at 20 °C until the reaction is complete (TLC monitoring, reaction times indicated in the corresponding Tables). After medium hydrolysis at 0 °C (sat. aq solution of $NaHCO_3$, 30 mL) and usual work-up, resulting crude *O*-formates are purified by preparative flash chromatography on silica gel Merck (45–60 μm) to afford the corresponding pure compounds (reaction times and conversion yields are indicated in the related Tables).

An Improved CH_2Cl_2/DCE-Based Experimental Procedure

$POCl_3$ or Tf_2O (1.1 mmol each O–Si bond in substrates) is dissolved in anhyd CH_2Cl_2 or $ClCH_2CH_2Cl$ containing anhyd DMF under nitrogen (CH_2Cl_2 or DCE/DMF: 2.0 mL/4.0 mmol, 320.0 μL), cooled at –15 °C, stirred for 30 min at the same temperature and added dropwise to a cold solution of *O*-silylated substrates (1.0 mmol, 1.0 mL of anhyd CH_2Cl_2 or DCE and 0.7 mL washing, 0 °C). The medium is then stirred at 20 °C for the indicated times (TLC monitoring). For trials including freshly distilled anhyd pyridine (2.5 mmol per O–Si bond, 200.0 μL), the base is added to the *O*-silylated substrate. After medium hydrolysis at 0 °C (biphasic mixture: sat. aq solution of $NaHCO_3$/Et_2O 10 mL/10 mL) and usual aqueous work-up, resulting crude compounds are purified by preparative flash chromatography on silica gel Merck (45–60 μm) to afford the corresponding pure *O*-formates (reaction times and conversion yields are indicated in Table 5).

Acknowledgement

The Bar-Ilan University and the Israeli Ministry of Immigrant Absorption are acknowledged for their financial support (internal research and laboratory equipment grants). The Rashi Foundation is thanked for its financial support to JPL (funding of a Guastella fellowship).

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