Reaction of carbohydrates with Vilsmeier reagent: a tandem selective chloro *O*-formylation of sugars†

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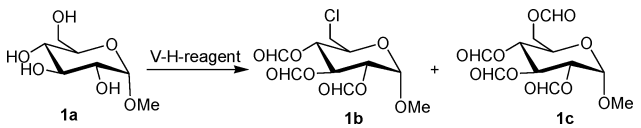
A convenient and efficient method for selective replacement of the primary hydroxyl groups of sugars by chlorine with concomitant *O*-formylation, compatible with the presence of a variety of functional groups, has been developed using the Vilsmeier–Haack reaction. Sugars having free primary hydroxyl groups mostly afforded the chloro-*O*-formylated product while sugars devoid of primary hydroxyl groups yielded only *O*-formylated products.

An efficient protecting group strategy is critical for achieving the synthesis of useful intermediates in carbohydrate chemistry.[1] Development of a strategy wherein more than one useful transformation can be carried out under the same reaction conditions without adding additional reagents and catalysts makes the process more advantageous and environmentally benign. In this respect, synthesis of the terminal chlorodeoxy sugars *via* direct substitution of hydroxyl groups by chlorine is of particular interest as they are in demand as precursors[2–5] for the synthesis of deoxy, amino-deoxy and unsaturated sugars and also as sweetening, anticarcinogenic, and potential male contraceptive agents. Similarly, *O*-formylation could be the method of choice for protecting sugar hydroxyl groups in a complex synthetic sequence because de-esterification can be effected selectively in the presence of other ester protecting groups e.g. a formate ester can be cleaved selectively in the presence of acetate and/or benzoate even in neutral alcoholic conditions.[6a] Further, if the alcohol group is planned to be oxidised later in a multistep synthetic scheme, the formylated alcohol can be directly oxidised under Oppenauer conditions.[6b] Moreover formate esters can also serve as intermediates for the preparation of glycopolymers.[6c,7]

Presently several methods are available for selective halogenation and *O*-formylation using different sets of reaction conditions. Garegg and Samuelsson[8] converted 3-hydroxy sugar derivatives to 3-deoxy-3-iodo sugars using triphenylphosphine, iodine and imidazole in toluene under reflux conditions, whereas Hanessian and Plessas[9] converted 1,2:5,6-di-*O*-isopropylidene D-glucofuranoside to the 6-bromo-6-deoxy derivative by treatment with *N*-bromosuccinimide and triphenylphosphine in *N*,*N*-dimethylformamide. Numerous other reagents have been developed for the *O*-formylation of sugar hydroxyl groups, such as formyl fluoride,[10] formic anhydride,[11] acetic–formic anhydride,[12] 2-(*N*-methyl-*N*-formylamino) pyridine,[13] dimethyl-chloromethyl-ammonium chloride,[13] *N*-formylbenzotriazole,[13] *N*,*N*-dimethylformamide,[14] HCOOH,[15] HCOOH–$HClO_4$,[16] HCOOH–BF_3·MeOH,[17] HCOOH–$Al(HSO_4)_3$,[18] and chloral–K_2CO_3[19] among many others.[20–22] Some applications that are pertinent to synthetic carbohydrate chemistry include the one step and selective conversion of silyl ethers of sugar derivatives into their corresponding formates using either PPh_3/CBr_4 in HCOOEt/H_2O[23] or Vilsmeier reagent,[24] and reaction of halomethyleniminium salts with various sugar alcohols to afford formate esters and chlorodeoxy sugars under different sets of experimental conditions. All these halo and formylating reagents have their limitations. As a result of the rather harsh experimental conditions such as medium acidity and higher temperatures and/or accompanying side reactions such as migration of isopropylidene rings,[9,25,26] none of them has given halo-deoxy *O*-formylated sugars exclusively. Moreover, to date there is only one report of tandem chlorination acetylation of sugar hydroxy compounds.[2,3]

The Vilsmeier–Haack (V–H) reaction (discovered 1927)[24] is recognized as one of the best methods for the direct formylation of electron-rich aromatic nuclei, enolizable ketones, enol ethers and other active hydrogen compounds. This reaction continues to receive wide attention in organic chemistry because of its simplicity and convenience. However according to our knowledge there is no report to date of one pot chloro-esterification under Vilsmeier conditions. In continuation of our research activities directed towards the development of one pot reaction strategies in carbohydrate chemistry,[27,28] we now disclose a novel method for the tandem one pot selective chloro-*O*-formylation of sugars.

We initially chose methyl glucoside **1a** as a model in order to evaluate the efficacy of chloroformylation using halomethyleniminium salt under different conditions (Scheme 1). Treatment of **1a** with DMF–$POCl_3$ complex (6 eq.) at 0 °C–rt indeed proceeded to completion in 1 h, but afforded a mixture of two products **1b** and **1c** in almost equal amounts.



Scheme 1

Compound **1b** was identified as methyl-2,3,4-tri-*O*-formyl-6-chloro-6-deoxy-α-D-glucopyranoside on the basis of NMR and

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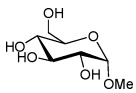
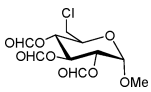
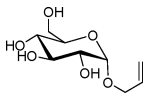
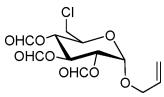
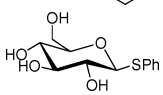
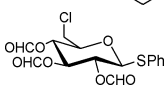
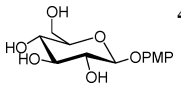
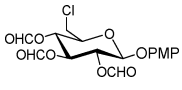
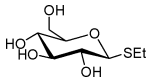
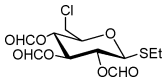
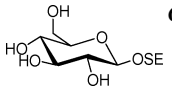
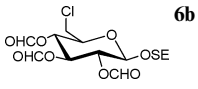
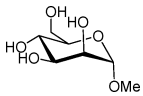
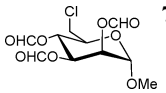
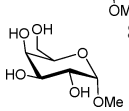
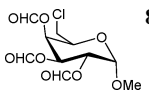
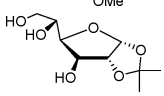
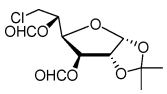
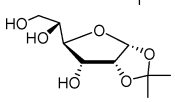
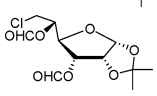
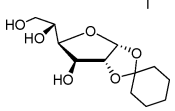
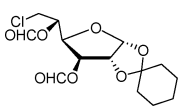
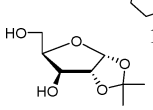
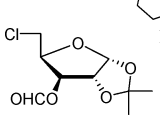
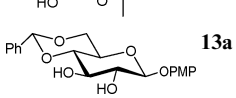
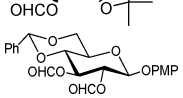
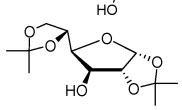
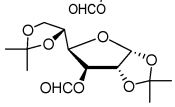
† Electronic supplementary information (ESI) available: Experimental procedures and characterizations, as well as ^1H and ^{13}C NMR spectra for compounds **1b–3b**, **7b**, **9b**. See DOI: 10.1039/b900026g

Table 1 Optimization of reaction conditions for methyl glucoside **1a**

Entry	Chlorinating agent	Ratio[a]	Temp (°C)	Time (h)	Yield[b] (**1b**)
1	DMF+$POCl_3$	1:6 eqv	0 to rt	0.5	50
2	DMF+$POCl_3$	1:6 eqv	0 to rt	1	55
3	DMF+$POCl_3$	1:10 eqv	0 to rt	1	70
3	DMF+$POCl_3$	1:6 eqv	0 to 60	1	55
4	DMF+$POCl_3$	1:10 eqv	rt to 60	6	85
5	DMF+$SOCl_2$	1:10 eqv	0 to rt	6	45
6	DMF+$SOCl_2$	1:10 eqv	rt to 60	6	45
7	DMF+PhCOCl	1:10 eqv	rt to 60	6	30
8	DMF+$(COCl)_2$	1:10 eqv	rt to 60	6	50

[a] Ratio between methyl glucoside and V–H-complex. [b] Yield obtained after column chromatography.

Table 2 Reaction of different sugar derivatives with V–H reagent

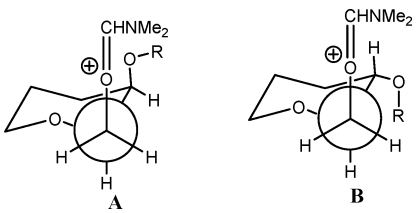
Entry	Substrate	Product[a]	Time[b] (h)	Yield (%)[c]
1	**1a** 	**1b** 	6	85
2	**2a** 	**2b** 	5	83
3	**3a** 	**3b** 	4	82
4	**4a** 	**4b** 	7	78
5	**5a** 	**5b** 	4	83
6	**6a**[f] 	**6b** 	8	82
7	**7a** 	**7b** 	7	72
8	**8a** 	**8b** 	5	25[d]
9	**9a** 	**9b** 	4	79
10	**10a** 	**10b** 	5	81
11	**11a** 	**11b** 	5	77
12	**12a** 	**12b** 	6	72
13	**13a** 	**13b** 	2	80[e]
14	**14a** 	**14b** 	1	91[e]

[a] Characterized by ^{1}H NMR and ^{13}C NMR (data available). [b] Total reaction time (sugar:V–H complex, 1:10). [c] Yield of the chloro-formylated product after column chromatography. [d] Performylated product obtained in major amount (65%). [e] Only performylated products obtained. [f] SE = 2-(trimethylsilyl)ethyl.

mass-spectral data. The signals for H-6,6′ and C-6 in the ^{1}H NMR and ^{13}C NMR spectra of **1b** were shifted upfield compared to those of the corresponding nuclei in the performylated product **1c** thereby indicating the introduction of the chlorine substituent at position 6. Using different chlorinating agents such as $SOCl_2$, oxalyl chloride and benzoyl chloride along with DMF at room temperature failed to improve the yield of **1b**. Gratifyingly, increasing the amount of the Vilsmeier reagent up to 10 equiv. afforded **1b** in 70% yield (entry no. 3, Table 1) but still failed to ensure the sole formation of **1b**.

To obtain **1b** as a sole product, modifications in experimental conditions were effected such as raising the temperature to 60 °C and also allowing more time (6 h) and this afforded **1b** in 85% yield along with only a trace amount of **1c**. In a separate control experiment treatment of **1c** with DMF–$POCl_3$ complex (6 eq.) at rt indeed afforded **1b** almost exclusively suggesting that the latter could be the thermodynamically controlled product.

Having optimized the reaction conditions,[29] the scope and generality of the method was explored. Initially the response of a free monohydroxyl sugar compound was investigated by using di-*O*-isopropylidene-α-D-glucofuranose (Entry 14, Table 2) which delivered only the *O*-formylated product. It may be noted that Hanessian and Plessas[4] failed to obtain such a product while working with dimethylchloroformiminium chloride. Further studies were performed using different polyhydroxy glycosides (Entries 1–8, Table 2) which were allowed to react with the V–H reagent under the optimized conditions and the results are summarized in Table 2. In all the cases the chloro-formylated products were obtained in good yield except with galactopyranoside where the *O*-formylated product was isolated with traces of the chloro-formylated product **8b**. It is noteworthy that the reaction proceeded smoothly without affecting other protecting groups. In all the cases chlorination took place selectively at the sterically less crowded primary hydroxy group of the sugar moiety leaving the secondary hydroxy groups, perhaps due to easy access of the bulky chloride ion. The anomalous behaviour of the galactose derivative can be rationalized as follows. The C_6–O bond needs to be oriented anti to the C_5–H for smooth attack by the chloride ion (Scheme 2). However this conformation is less favoured in the galactose series (Newman projection-A) than in the glucose series (Newman projection-B) due to torsional strain involving the axial C_4–OR group in the case of the former. Therefore the galactose substrate furnishes the performate as the major product. With the exception of galactosides our results clearly show that compounds having primary hydroxyl groups afforded the chloro-formylated product.



Scheme 2

Conclusions

In conclusion, a method for tandem one pot selective chloro-*O*-formylation of sugars has been developed utilizing the Vilsmeier–Haack reaction conditions. It offers operational simplicity and proceeds with moderate to high yields. This together with the enormous importance of the downstream products in the synthesis of glycopolymers and glycoconjugates establishes the utility of the method.

Acknowledgements

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28 D. Mukherjee, K. S. Yusuf and S. C. Taneja, *Org. Lett.*, 2008, **10**, 4831.
29 **Typical procedure for chloro-*O*-formylation:** A stirred, cooled DMF solution of the complex $POCl_3$/DMF (prepared from 1.52 g $POCl_3$, in 5 mL anhydrous DMF, 0 °C) was added dropwise to a cold solution of α-D-methyl-glucopyranoside (0.2 g, 1.0 mmol in 10 mL DMF) under an inert atmosphere. The mixture was then agitated at 60 °C and the reaction monitored by TLC. After completion of the reaction (reaction

time given in table-2) the contents were treated with saturated $NaHCO_3$ solution (30 mL), then extracted with solvent ether (4 × 30 mL), the organic solvent was evaporated, and the crude product was purified by column chromatography over silica gel to afford a syrupy mass. **Methyl 6-chloro-2,3,4-tri-*O*-formyl-α-D-glucopyranoside (1b)**. Anal. calc. for $C_{10}H_{13}ClO_8$: C, 40.49; H, 4.42; Cl, 11.95. Found: C, 40.52; H, 4.49; Cl, 11.99. MS (%) M^+ at m/z 297. $[\alpha]_D^{26}$ +60.0 (*c* 1.0, $CHCl_3$); δ_H (500 MHz; $CDCl_3$; Me_4Si); δ 3.47 (s, 3H, OCH_3), 3.59 (dd, 1H, J = 12.2, 6.1 Hz, H-6^a), 3.69 (dd, 1H, J = 12.2, 2.4 Hz, H-6^b), 4.10 (ddd, 1H, J = 9.6, 6.1, 2.4 Hz, H-5), 5.03–5.05 (m, 1H, H-2), 5.08 (d, 1H, J = 3.4 Hz, H-1), 5.23 (t, 1H, J = 9.6 Hz, H-3/H-4), 5.69 (t, 1H, J = 9.5 Hz, H-3/H-4), 8.05 (s, 2H, 2×CHO), 8.08 (s, 1H, CHO). ^{13}C NMR (75 MHz, $CDCl_3$): δ 43.6, 56.1, 68.9, 69.2, 69.6, 71.5, 96.7, 159.9, 160.7, 160.9.