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Application of Polymer-Supported Electrophilic Reagents for the 1,2-Functionalization of Glycals

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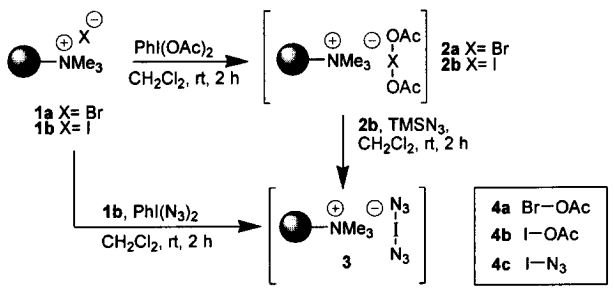
Abstract: Polymer-supported electrophilic reagents are prepared which efficiently add to carbohydrate-derived glycals under very mild conditions. Depending on the hypervalent reagent initially employed for oxidizing polymer-bound halides **1a** or **1b** both acetoxyhalogenations or azidoiodination can be carried out. With sugar-derived glycals, 2-deoxy-2-halo-pyranosyl acetates or azides are generated in excellent yield. Free hydroxy groups are tolerated. Even, fully unprotected glucal **23** can be employed for the short synthesis of 2-deoxy-2-iodo glycosyl acetates **24a,b**.

The rapidly increasing interest in polymer-bound reagents is evidenced by numerous recent publications on this topic including some reviews.[1] The major advantage of these materials lies in the simple purification typically associated with solid-phase organic synthesis which is combined with the flexibility of solution-phase chemistry. Furthermore, these reagents may be used in excess in order to drive the reaction to completion. Until recently, no polymer-supported reagents that perform the 1,2-cohalogenation[2] of alkenic double bonds were known. Our interest in new electrophilic halogen-ate(I) complexes[3] has led to the development of new electrophilic polymer-bound reagents.[4] In this communication, we describe their preparation and synthetic power in 1,2-cohalogenations of carbohydrate-derived glycals.

Scheme 1



Synthesis of these reagents was achieved by diacyloxy-iodobenzene promoted oxidation of polystyrene-bound halides **1a,b** which presumably gave polymer-supported di(acyloxy)halogen-ate(I) anions **2a** and **2b**.[5] These reagents act as immobilized acylated hypobromite **4a** or hypoiodite **4b**. Furthermore, the acetoxy groups in **2b** were substituted by azide with $TMSN_3$ affording resin **3**.[4] In this case, the active reagent synthetically behaves like immobilized iodine azide (**4c**). It may also be generated by direct azido transfer after treatment of **1b** with bisazido iodo benzene.[6] All resins are not deactivated by extensive washing so that it is reasonable to propose

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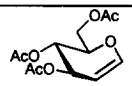
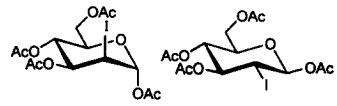
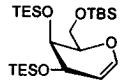
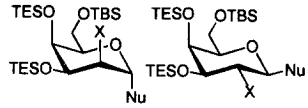
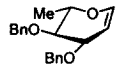
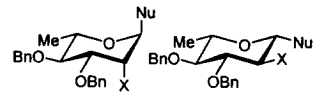
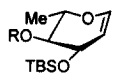
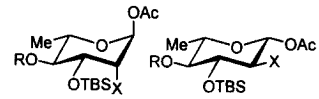
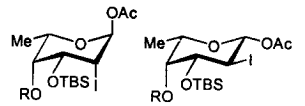
that polymer-bound iodate(I) complexes **2a,b** and **3** are the active species. In reactions with glycals, the expected 1,2-addition products like the 2-deoxy-2-iodo-pyranosyl acetates are ideally suited as glycosyl donors for the

Table 1: 1,2-Functionalization of glycals promoted by polmer-bound electrophilic reagents **2** and **3**.

	alkene		polymer (eq), conditions[a]	1,2-addition products	Nu	ratio[b] (α : β)	yield (%)
5			**2b** (4), CH_3CN, 12h		**12**	1 : 2.4	92
6			**2b** (4), CH_2Cl_2, 12h **3** (4) CH_2Cl_2, 12h		**13** Nu= Ac **14** Nu= N_3	1 : 2 1 : 9	92 82
7			**2a** (4), CH_2Cl_2, 12h **2b** (3), CH_2Cl_2, 12h **3** (4), CH_2Cl_2, 12h		**15** Nu= Ac **16** Nu= Ac **17** Nu= N_3	1 : 2 1.5: 1 1 : 1	97 96 86
8		R= TBS	**2a** (3), CH_2Cl_2, 12h **2b** (3), CH_2Cl_2, 12h		**18** **19**	2 : 1 1.2: 1	97 98
9		R= H	**2b** (4), CH_2Cl_2, 6h **2b** (4), CH_3CN, 6h **2b** (4), toluene, 6h		**20**	2.5: 1 2.5: 1 2.7: 1	83 91 90
10		R= TBS	**2b** (4), CH_2Cl_2, 12h		**21**	1 : 1	97
11		R=H	**2b** (4), CH_2Cl_2, 6h **2b** (4), CH_3CN, 6h **2b** (4), toluene, 6h		**22**	1 : 9 1 : 4.2 1 : 3.5	88 95 91

[a] The number of equivalents refer to halide anions in starting **1**. All reactions were carried out at room temp. [b] Determined from ^1H NMR spectra.

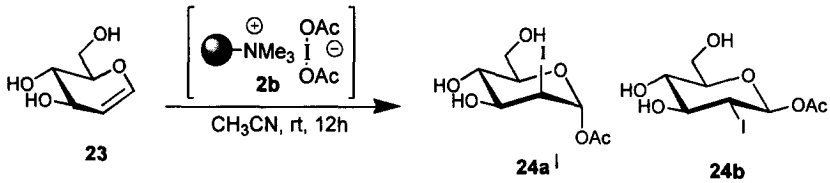
preparation of 2-deoxy-oligosaccharides.[7] In addition, glycosyl azides that would be generated from azidoiodination of glycals can serve for the synthesis of the corresponding glycopeptides.

A preliminary experiment with tri-*O*-acetyl-D-glucal (**5**) demonstrated that **2b** smoothly promotes 1,2-*trans*-acetoxyiodination of the enolether double bond to yield the corresponding 2-deoxy-2-iodo-glycosyl acetates **12**. Unlike classical reagents for acetoxyiodination of alkenes, use of a reagent **2b** does not require glacial acetic acid[8] or heavy metals.[9] In a similar manner, reaction of glycals **6** - **11** with the new reagents **2a,b** and **3** afforded 1,2-*trans* addition products **13** - **22** in different solvents with excellent yields (Table 1).[10] In most cases, filtration and removal of the solvent *in vacuo* afforded pyranosyl acetates[11] and pyranosyl azides with high purity. Chromatographic methods were required for separating diastereoisomers. The reagents are employed in excess with reference to the specified amount of halide in **1a** and **1b**. This observation may be rationalized by

assuming that only a proportional amount of immobilized halide was transformed into the hypervalent reagent. Partially protected glycals like compounds **9** and **11** smoothly react to the corresponding 1,2-addition products **20** and **22**.[12] Thus, hydroxy groups are tolerated and do not add to the intermediate iodonium ions to form disaccharides. The pronounced *trans*-selectivity observed for the bromoacetoxylation of *arabino*-configured glycals **7** and **8** partly contrast selectivities observed for soluble di(acyloxy)bromate (I) ammonium salts. In this latter case, we encountered both 1,2-*trans* as well as *cis*-addition to the enolether double bond.[3b] The synthesis of 1,2-addition products is initiated by an electrophilic halonium species which adds both to the α- as well as the β-face of the enolether double bond. The resulting cyclic halocarbonium ion which is strongly favored commonly reacts further to 1,2-*trans* products after capture by the acetate or azide anions. *Lyxo*-configured glycals **6** and **11** containing a medium or small sized pseudoaxial substituent at C-4 are preferentially attacked from the α-face by the electrophilic reagents which results in valuable β-*galacto*-configured 1,2-addition products **13**, **14** and **22**.[13] However, for fully *O*-silylated L-fucal **10** this selectivity is deleted which we ascribe to an altered, presumably an inverted half-chair or twist-boat conformation of the starting glycal.[14] Finally, an all *trans*-orientation at C3 - C5 as present in glycals **5** and **7** - **9** does not favor formation of a single diastereoisomer or at best only moderate preference for the *trans*-diaxial addition products α-**12** and **15** - **20**.

Remarkably, even fully unprotected glycal **23** can undergo a 1,2-cohalogenation with the polymer-supported reagent **2b** to furnish pyranosyl acetates **24a,b** in 71% isolated yield and in a 2.5 : 1 ratio (Scheme 2).

Scheme 2



In summary, we described a new class of polymer-supported electrophilic reagents which can efficiently be employed for acetoxyhalogenation reaction as well as azidoiodination of carbohydrate-derived glycals. These reagents should ideally be suited for automated parallel synthesis of glycosyl donors.

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References and Notes

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4. Kirschning, A.; Monenschein, H.; Schmeck, C., *Angew. Chem.* **1999**, *111*, 2720-2722; *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 2594-2596.
5. *General procedure for the preparation of polymer-bound reagents* ***2a, b:*** A suspension of polymer bound halide (3.2 g/mmol for bromide; 2.9 mmol/g for iodide) and $PhI(OAc)_2$ (1.8 eq.) in dry CH_2Cl_2 (3 ml/ mmol halide anion) under nitrogen, which was protected from light, was shaken at 300 rpm for 6 h. Filtration and washing of the resin with CH_2Cl_2 (3x) and dried *in vacuo* to afford the title reagents.
   General procedure for the preparation of polymer-bound reagent ***3:*** A suspension of **2b** (one theoretical eq.) in CH_2Cl_2 (3 ml / mmol) was treated with $TMSN_3$ (2.6 eq) under nitrogen, which was protected from light, was shaken at 300 rpm for 6 h. Filtration and washing of the resin with CH_2Cl_2 (3x) and dried *in vacuo* to afford the title reagents.
6. As $PhI(N_3)_2$ has to be prepared *in situ* from $PhI(OAc)_2$ and $TMSN_3$ efficient azidotransfer onto **1** is hampered by the presence of trimethylsilyl acetate.
7. (a) Kirschning, A. Bechthold, A.; Rohr, J., *Top. Curr. Chem.* **1997**, *188*, 1-84. (b) Toshima, K.; Tatsatu, K., *Chem. Rev.* **1993**, *93*, 1503-1531.
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10. *General procedure for the 1,2-cohalogenation of alkenes:* A mixture of alkene (1 eq) and resin were shaken at 300 rpm under light protection in dry solvent (1.5 ml / mmol; for eq of reagent and solvents refer to Table 1) at rt. Completion of the reaction was monitored by tlc. Filtration terminated the reaction. The resin was washed with CH_2Cl_2 (3x) and the combined organic washings and filtrate were concentrated under reduced pressure. In some cases, further purification by column chromatography was necessary. Finally, the polymer was recycled into the iodide form by treatment with concentrated HI for 1 h at rt.
11. For acetoxyiodination of glycals and glycal esters see: (a) Roush, W. R.; Briner, K.; Sebesta, D. P., *Synlett* **1993**, 264-266. (b) Kosma, P.; Sekljic, H.; Balint, G., *J. Carbohydr. Chem.* **1996**, *15*, 701-714. (c) Lafont, D.; Boullanger, P.; Carvalho, F.; Vottero, P., *Carbohydr. Res.* **1997**, *297*, 117-126. (d) Lafont, D.; Boullanger, P.; Rosenzweig, M., *J. Carbohydr. Chem.* **1998**, *17*, 1377-1393.
12. The spectroscopic properties of all new compounds are in agreement with the assigned structures.
    Selected physical and spectroscopic data for **22**: colourless oil; $[\alpha]_D^{21}$ -50.8 (c= 1, $CHCl_3$); ^1H NMR ($CDCl_3$):δ 5.77 (1H, d, J= 9.3, 1-H), 4.0 (1H, dd, J= 10.2, 9.3, 2-H), 3.88 (1H, dd, J= 10.2, 3.2, 3-H), 3.76 (1H, dq, J= 6.3, 0.8, 5-H), 3.47 (1H, dd, J= 3.2, 0.8, 4-H), 2.42 (1H, br, OH), 2.12 (3H, s, O_2CCH_3), 1.34 (3H, d, J= 6.3, 6-H), 0.94 (9H, s, *t*Bu), 0.3, 0.14 [6H, 2s, $Si(CH_3)_2$], ^{13}C NMR ($CDCl_3$) δ: 169.1 (C=O), 94.3 (C-1), 76.8, 72.0, 71.3 (C-3, C-4, C-5), 32.1 (C-2), 25.8 [$(CH_3)_3$], 20.8 (OAc), 18.0 (*t*Bu), 16.1 (C-6), -4.2, -4.4 [$Si(CH_3)_2$].
13. When the reagent system Et_4NI and $PhI(OAc)_2$ is employed instead glycals **6** and **11** afford 2-deoxy-2-iodo-glycosyl acetates **13** and **22** with similar preference for the *lyxo*-configured isomers.
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