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Efficient and direct synthesis of saccharidic 1,2-ethylidenes, orthoesters, and glycals from peracetylated sugars via the in situ generation of glycosyl iodides with I_2/Et_3SiH☆

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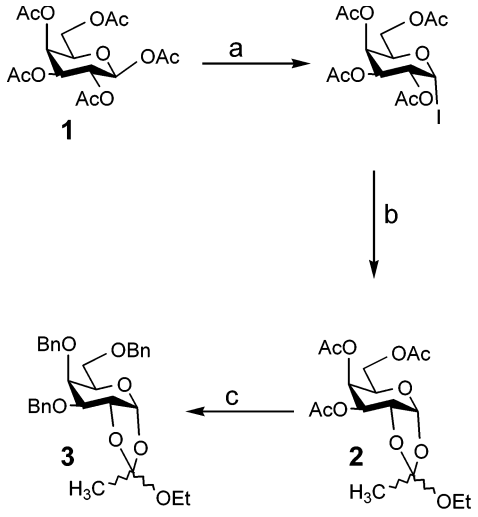
Abstract—Peracetylated sugars can be efficiently converted into the corresponding 1,2-ethylidenes, -orthoesters, and -glycals via the in situ generation of glycosyl iodides promoted by I_2/Et_3SiH. The approach is straightforward and avoids isolation of the sensitive iodinated intermediates.

For a long time, glycosyl iodides have been considered impractical reagents in carbohydrate chemistry due to their instability. However, in recent years these derivatives have attracted some interest and a variety of approaches have been published for their synthesis. For example, glycosyl iodides have been prepared by treatment of the corresponding hemiacetals with iodoenamines[1] or with a complex of polystyryl phosphine and iodine.[2] These compounds can also be prepared from glycosyl acetates with hydriodic acid in acetic acid,[3] and catalytic BiI_3 with an excess of alkyl silyl iodides.[4] Quite recently, a practical access to glycosyl iodides from the corresponding 1-*O*-acetylated derivatives has been described by Gervay and co-workers.[5] This procedure is based on the use of TMSI and takes advantage of the easy removal of volatile by-products. The same research group has shown the feasibility of using the donors obtained in the synthesis of *O*-, *C*-, and *N*-glycosides exploiting either a direct displacement[6] or an α-selective glycosidation based on the in situ anomerization promoted by tetrabutylammonium iodide.[7] As an alternative to the unstable and expensive TMSI, Koreeda reported a protocol for conversion of glycosyl acetates into iodides based on the in situ generation of anhydrous HI through the combination of cheaper and more stable coreagents such as iodine and thiolacetic acid (or 1,3-propandithiol).[8] More recently, in the course of our investigations on the use of the I_2/Et_3SiH reagent as a glycosidation promoter, we found as an ancillary result that this combined system could be an alternative to the latter approach[9] avoiding the use of malodorous thiols, whose nucleophilic character could also give undesired



Scheme 1. Synthesis of orthoester **3**. *Reagents and conditions*: (a) I_2 (1.4 equiv.), Et_3SiH (1.4 equiv.), CH_2Cl_2, reflux, 30–60 min; (b) lutidine (4 equiv.), EtOH (6 equiv.), $(Bu_4N)Br$ (0.4 equiv.), rt, overnight; (c) KOH, toluene, reflux, then BnBr.

Keywords: glycosyl iodides; orthoesters; glycals; ethylidenes.

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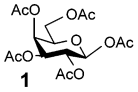
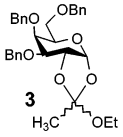
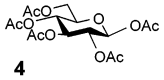
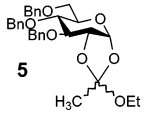
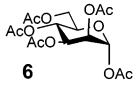
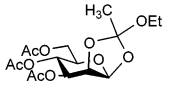
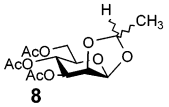
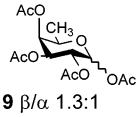
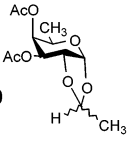
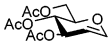
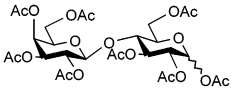
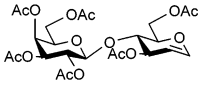
side-reactions.[8] In this paper we wish to report the exploitation of this approach for the one-pot conversion of easily prepared and commercially available peracetylated sugars into widely used saccharidic building blocks such as 1,2-orthoesters, 1,2-ethylidenes and 1,2-glycals. These intermediates are typically prepared from the corresponding glycosyl bromides, whose synthesis from the corresponding 1-*O*-acetylated precursors requires quite demanding experimental conditions.[10]

This investigation was inspired by a problem associated with the synthesis of the intermediate **3** starting from acetobromo galactose, which can be achieved by conversion into orthoester **2**, via halide-promoted anomerization (lutidine, ethanol and tetrabutylammonium bromide),[11] followed by deacetylation and benzylation. Exploiting this procedure compound **3** was obtained in good overall yield (56% for three steps).

To avoid the use of the relatively expensive acetobromo galactose, a new synthesis of **2** was developed starting from the cheaper pentaacetyl galactose **1** (Scheme 1). Treatment of this with 1.4 equivalents of I_2 and Et_3SiH in refluxing dichloromethane produced the corresponding α-iodide (TLC and NMR analysis of an aliquot of the crude reaction mixture). Lutidine, ethanol, and tetrabutylammonium bromide were then added and the mixture was left stirring overnight. NMR analysis of the crude material showed the formation of the desired orthoester derivative. The crude mixture was subjected to the one-pot deacetylation–benzylation sequence to afford compound **3** in a 50% overall yield (over four steps) with a single chromatographic purification (Scheme 1, Table 1, entry 1).

Table 1. Conversion of peracetylated sugars into 1,2-orthoesters, -ethylidenes, and glycals

Entry	Reagent	Procedure[a]	Product[b]	Overall yield (%)
1	 **1**	A	 **3**	50
2	 **4**	A	 **5**	58
3	 **6**	B	 **7**	71
4	**6**	C	 **8**	66
5	 **9** β/α 1.3:1	C	 **10**	64
6	**4**	D	 **11**	81
7	**9**	D	 **12**	47
8	 **13** α/β 5:1	D	 **14**	71

[a] Procedure A: See Scheme 1.

Procedure B: I_2 (1.4 eq), Et_3SiH (1.4 eq), CH_2Cl_2, reflux, 30-60 min; lutidine (4 eq), EtOH (6 eq), tetrabutylammonium bromide (0.4 eq), overnight, r.t.

Procedure C: I_2 (1.4 eq), Et_3SiH (1.4 eq), CH_2Cl_2, reflux, 30-60 min; then removal of the solvent and addition of $NaBH_4$, CH_3CN, r.t., 2-4 h.

Procedure D: I_2 (1.4 eq), Et_3SiH (1.4 eq), CH_2Cl_2, reflux, 30-60 min; then extractive work-up and addition of Cp_2TiCl_2 (2.5 eq), Mn (5 eq), THF, r.t., 2-5 hours.

[b] All products were identified by ^1H and ^{13}C NMR spectroscopy (see supplementary material).

The application of this strategy has been investigated for the synthesis of a variety of useful saccharidic building-blocks commonly prepared from peracetylated glycosyl bromides. For example, the same synthetic sequence was also applied to the gluco precursor **4** in good overall yield (entry 2). It should be noted that the orthoesterification reaction can be accomplished via a one-pot procedure without any work-up of the iodination mixture, in contrast to the corresponding synthesis via glycosyl bromides. In addition, the efficacy of the whole synthetic sequence was not compromised by the use of unpurified intermediates. The acetylated orthoester **7** was prepared from the corresponding peracetylated *D*-mannose derivative **6** via an analogous one-pot sequence of anomeric iodination and orthoesterification (entry 3). The sequence afforded the product as a single diastereoisomer in 71% overall yield after the final chromatographic purification.

Another interesting application of the protocol is represented by the synthesis of 1,2-ethylidenes, another class of very useful precursors in carbohydrate chemistry. These derivatives are routinely prepared by treating glycosyl bromides with excess $NaBH_4$, and (for *gluco*- and *galacto*-derivatives) catalytic tetrabutylammonium bromide in acetonitrile.[12] The synthesis of these compounds directly from peracetylated precursors has been demonstrated starting from mannose and fucose derivatives (entries 4 and 5, respectively). In these cases, after the generation of the glycosyl iodide the initial solvent (dichloromethane) was removed and replaced with acetonitrile, then sodium borohydride and (only for entry 5) tetrabutylammoniun bromide were added. Also in this case the one-pot sequence gave a useful yield with minimization of the experimental operations. In addition, the generation of 1,2-ethylidenes from the intermediate glycosyl iodide turned out to be a faster process than in the case of brominated intermediates.

A further application has been evaluated in the synthesis of 1,2-glycals (entries 6-8). In this case the iodination mixture was worked-up by a simple extraction and the crude product from the organic phase was directly subjected to elimination conditions as described for anomeric bromides by Skrydstrup and co-workers (Cp_2Cl_2Ti and manganese in THF).[13] Also in this case the elimination step required typically much shorter times than with the corresponding glycosyl bromides (2-4 h instead of more than 10 h).[13] A practical application of this approach was demonstrated in the synthesis of the expensive lactal derivative **14** (entry 8).

In conclusion, an efficient procedure for the synthesis of glycosyl iodides based on the use of cheap and easily handled reagents has been described.[14] These intermediates can be efficiently converted into 1,2-orthoesters or -ethylidenes via a one-pot approach, while 1,2-glycals can be readily obtained after a simple extractive work-up of the iodination mixture.[14]

Supplementary material: Spectral data (^1H and ^{13}C NMR) for all products in Table 1 are available.

Acknowledgements

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14. **General procedure for the synthesis of glycosyl iodides**: the peracetylated sugar (2 mmol) was coevaporated with dry toluene and then dissolved in anhydrous dichloromethane (6 mL). To the solution were added I_2 (711 mg, 2.8 mmol) and triethylsilane (450 μL, 2.8 mmol). The mixture was refluxed until TLC analysis displayed complete consumption of the peracetylated sugar (the glycosyl iodides are partially unstable on TLC, especially in the case of the fucose derivative), and then submitted to further reactions.
General procedure for preparation of 1,2-orthoesters. To the above reaction mixture were sequentially added lutidine (930 μL, 8 mmol), ethanol (680 μL, 12 mmol) and tetrabutylammonium bromide (258 mg, 0.8 mmol). The mixture was left to stir overnight at rt (in the case of *galacto*- and *manno*-derivatives) or refluxed for 4 h (*gluco* derivative). When the reaction was complete (TLC), the mixture was concentrated and chromatographed on silica gel (entry 3) or directly submitted to the deacetylation–benzylation one-pot procedure (entries 1 and 2).

General procedure for preparation of 1,2-ethylidenes. Following the above described synthesis of the glycosyl iodide intermediate, dichloromethane was removed with a stream of nitrogen. The residue was dissolved in acetonitrile, and then sodium borohydride (378 mg, 10 mmol) and tetrabutylammonium bromide (258 mg, 0.8 mmol) (only for entry 6) were sequentially added (NOTE: exothermic reaction). On completion of the reaction (TLC), the mixture was diluted with dichloromethane and washed with water. Concentration of the organic phase afforded a residue that was purified by silica gel chromatography.

General procedure for preparation of 1,2-glycals. Following the above described synthesis of the glycosyl iodide intermediate, the mixture was diluted with dichloromethane and washed with a 5% solution of sodium bicarbonate containing sodium thiosulfate (in the minimal amount necessary to reduce the residual iodine). The organic phase was dried and concentrated. The residue was dissolved in THF (5 mL) and Cp_2Cl_2Ti (1.25 g, 5 mmol) and manganese (50 mesh, 550 mg, 10 mmol) were added at room temperature under argon. After completion of the reaction (TLC) the mixture was concentrated and the residue chromatographed on silica gel.