Activation of Glycosyl Phosphates by in situ Conversion to Glycosyl Iodides under Neutral Conditions in Concentrated Solutions of Lithium Perchlorate in Organic Solvents

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Abstract: Glycosyl phosphates are converted in situ into glycosyl iodides and thereby advantageously employed as glycosyl donors under mild neutral conditions by treatment with LiI in 1M solutions of $LiClO_4$ in organic solvents. Copyright © 1996 Elsevier Science Ltd

Glycoconjugates have crucial functions in numerous biological processes, i.e. they mediate cell-cell adhesion and communication and they are the characteristic determinants of the human blood group system and of so-called tumor associated antigens.[1] In the light of these important roles the development of efficient methods for the synthesis of tailor made complex glycosides, which could, for example, be used to study these biological processes, is of great importance to synthetic[2] and medicinal chemistry.[3]

Reliable routes for the construction of glycosides are the diverse variants of the Koenigs-Knorr reaction in which glycosyl halides must be activated by heavy metal salts.[2] In particular, the use of glycosyl bromides and chlorides in combination with silver or mercury salts belongs to the well established and reliable techniques of carbohydrate chemistry since these glycosyl donors on the one hand are reasonably stable and on the other hand can be activated under mild conditions. In principle, the use of glycosyl iodides would be highly desirable since these activated carbohydrate derivatives display a significantly higher reactivity than the corresponding bromides and chlorides. However, with a few exceptions[4,5] glycosyl iodides could not be applied advantageously in saccharide synthesis since they are too unstable to be handled and stored with the required reliability[6] and often have to be prepared under drastic conditions, i.e. by treatment of appropriate precursors with trimethylsilyl iodide[7] or HI in acetic acid.[8]

As alternatives to the classical Koenigs-Knorr process the use of glycosyl trichloroacetimidates, thioglycosides, glycosyl phosphites and glycosyl phosphates was developed recently.[2] Of these glycosyl donors in particular the glycosyl phosphates are readily accessible and stable reagents. However, their reactivity in O-glycoside syntheses is only moderate so that they were applied in only a few cases.[9] Therefore, the development of methods for the activation of glycosyl phosphates under mild conditions is highly desirable.

We have recently described that the detachment of different leaving groups from the anomeric center of carbohydrates can be induced by employing concentrated solutions of $LiClO_4$ in organic solvents as reaction media which stabilize polar or ionic intermediates.[10] The purpose of this paper is to report that under these mild neutral conditions glycosyl phosphates can be activated by means of their in situ conversion to glycosyl iodides. These glycosyl donors then react smoothly with different glycosyl acceptors to give O-glycosides without the need to use any further promoter, e.g. a heavy metal salt.

In order to investigate if glycosyl iodides can be generated in situ from other carbohydrate derivatives, in orienting experiments the α-chloride, -bromide, -trichloroacetimidate and -diphenylphosphate of benzyl protected
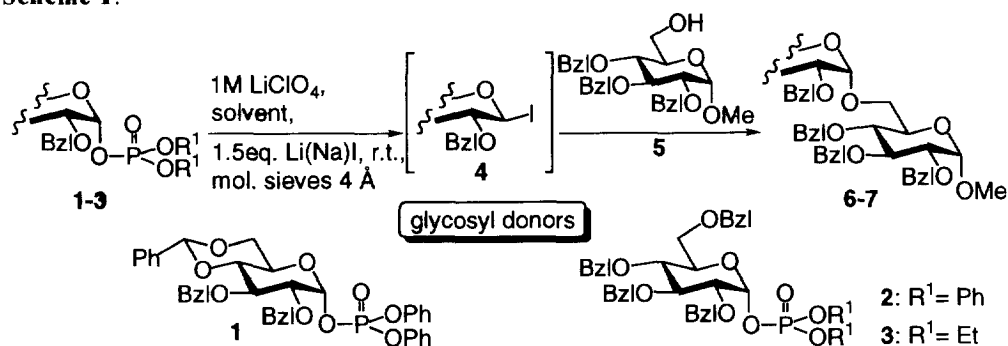
Scheme 1:

Table 1: Results of the Glycosylations employing the Glycosyl Phosphates 1-3 as Glycosyl Donors in LiClO$_4$/ CH$_2$Cl$_2$ Solutions in the Presence of Iodide Salts.

Entry	Glycosyl Donor	R^1	Product	Iodide Salt	Solvent	Yield [%][a)	Anomeric Ratio[b) α:β
1	1	Ph	6	LiI	CH$_2$Cl$_2$	44	15:1
2	1	Ph	6	NaI	CH$_2$Cl$_2$	40	7:1
3	2	Ph	7	LiI	CH$_2$Cl$_2$	63	3:1
4	3	Et	7	LiI	CH$_2$Cl$_2$	45	5:1
5	3	Et	7	I	CH$_2$Cl$_2$	8	1:1
6	2	Ph	7	LiI	CH$_3$CN	54	2:1
7	2	Ph	7	I	CH$_3$CN	83c	1:3

a) Based on chromatographically purified glycoside **6,7**. All glycosides **6,7** were identified by [1]H- and ^{13}C nmr spectroscopy (250- or 400 MHz; CDCl$_3$); b) Determined by integration of the relevant signals in the ^{1}H nmr spectra; c) 0.25 M LiClO$_4$ in CH$_3$CN was employed.

glucose were treated with lithium iodide in a 1M solution of LiClO$_4$ in CH$_2$Cl$_2$ in the presence of a glycosyl acceptor. Whereas under these conditions glycoside formation was induced with several of the glycosyl donors employed the best results were obtained with the diphenylphosphate **2** so that we examined the use of phosphate esters as leaving groups at the anomeric center in greater detail.

If the glycosyl phosphates **1** to **3** are treated with the 6-O-deprotected glucose derivative **5** in solutions of LiClO$_4$ in CH$_2$Cl$_2$ in the presence of 1.5 equivalents of an iodide salt the disaccharides **6** and **7** are formed under neutral conditions in 40-63% yield with the α-anomers predominating (Scheme 1, Table 1). We assume that the reaction proceeds via initial attack of the iodide on the α-configured glycosyl phosphates **1-3** to give rise to the very reactive β-glycosyl iodides **4** which then are activated in the LiClO$_4$ solution and attacked by the glycosyl acceptor to give predominantly the α-anomers of the saccharides **6** and **7**. This assumption is supported by the observation that in the absence of an iodide salt **2** reacts with different alcohols in 1M solutions of LiClO$_4$ in CH$_2$Cl$_2$ to give β-glycosides in excess,[10] i.e. without an inversion of the configuration of the anomeric center prior to the glycoside bond formation. More convincingly an unstable glycosyl iodide derived from **1** could be isolated from the reaction mixture and was unambiguously identified by [1]H- and ^{13}C nmr spectroscopy.[11]

In accordance with the observations made in glycoside syntheses in LiClO4/solvent mixtures without the addition of iodide salts the best results for the synthesis of **6** and **7** were obtained in 1M solutions of LiClO4. The most advantageous solvents are CH2Cl2 and CH3CN, in ether the yields of the glycosylations are substantially lower. The use of LiI or NaI results in comparable yields of the products but in the presence of LiI the stereoselectivity of the glycoside formation is higher (Table 1, entries 1 and 2). In both CH2Cl2 and CH3CN the α-anomers predominate due to the intermediate formation of the β-iodide which is attacked preferably from the axial direction with inversion of configuration. This is illustrated by the observation that in this solvent system in the absence of LiI the β-anomers are formed in excess due to participation of the solvent in the glycosylation reaction[10,12] (Table 1, compare entries 3 and 6 with entry 7). The nature of the alcohols present in the phosphate leaving group may influence the result of the glycosylation reaction. Thus, the more reactive diphenyl phosphate **2** gives the desired glycoside **7** with higher yield but with lower α selectivity than the diethyl phosphate **3** (Table 1, entries 3 and 4). The low intrinsic reactivity of the glycosyl donors employed under the above mentioned conditions is apparent from the fact that in the absence of LiI but under otherwise identical conditions the glycoside **7** is formed from **3** in only 8% yield (Table 1, entry 5).

In order to determine the scope of the glycosylation method delineated above the glycosyl phosphate **2** was treated with the glycosyl acceptors **8**, **9** and **10** in 1M solutions of LiClO4 in CH2Cl2 in the presence of 1.5 equivalents of LiI (Scheme 2, Table 2). In the ensuing reactions the galactosyl disaccharide **11**, the serine
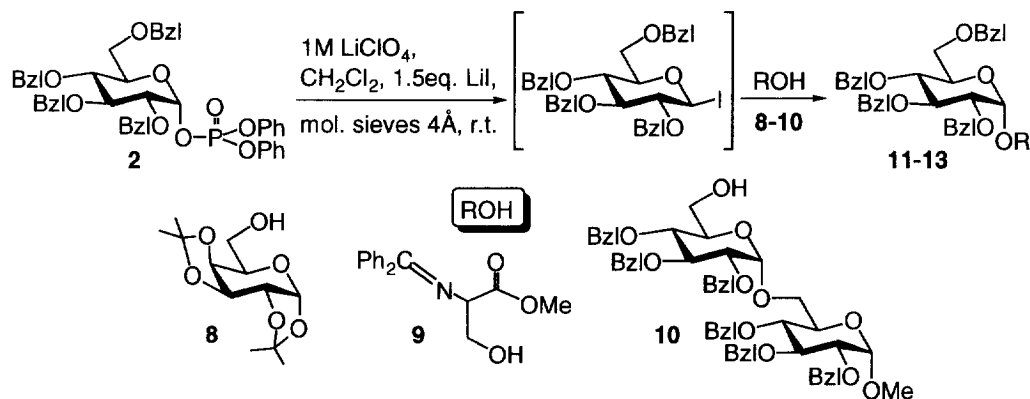
Scheme 2:

Table 2: Results of the Glycosylations employing the Phosphate **2** as Glycosyl Donor in 1M LiClO4/CH2Cl2 Solutions in the Presence of 1.5eq. of LiI.

Entry	Glycosyl Acceptor	Product	Yield [%][a]	Anomeric Ratio[b] α:β
1	**8**	**11**	45	3:1
2	**9**	**12**	54	3:1
3	**10**	**13**	46	only α

a) Based on chromatographically purified glycoside **11-13**. All glycosides **11-13** were identified by [1]H- and ^{13}C nmr spectroscopy (250- or 400 MHz; CDCl3); b) Determined by integration of the relevant signals in the ^{1}H nmr spectra

glycoside **12** and the glucosyl trisaccharide **13** were formed in preparatively useful yields and with the α-anomers predominating. Particularly remarkable is the finding that in the case of the disaccharide acceptor **10** the desired trisaccharide **13** was obtained with complete stereoselectivity (Table 2, entry 3).

In conclusion we have demonstrated that glycosyl phosphates can be activated by their in situ conversion to glycosyl iodides in 1M solutions of $LiClO_4$ in CH_2Cl_2 in the presence of LiI. These seemingly too unstable glycosyl iodides can advantageously be employed in glycosylation reactions under neutral conditions and without the addition of further promoters. They react smoothly with glycosyl acceptors being derived from different monosaccharides, disaccharides and amino acid derivatives. These findings should open up new opportunities for carbohydrate chemistry and their application to the selective construction of complex and sensitive glycoconjugates is actively being pursued in our laboratories.

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11. 2,3-Di-O-benzyl-4,6-O-benzylidene-α-D-glucosyl iodide obtained from **1**: 400 MHz ^{1}H nmr (CDCl₃): δ = 2.87 (dd, $J_{1,2}$ = 4.2Hz, $J_{2,3}$ = 8.8Hz, 1H, 2-H), 3.73-3.81 (m, 2H, 4-H, 6-H_a), 3.92-3.40 (m, 2H, 3-H, 5-H), 4.30 (dd, $J_{5,6b}$ = 4.8Hz, $J_{6a,6b}$ = 10.2Hz, 1H, 6-H_b), 4.71- 4.89 (m, 4H, CH_2-Ph), 5.55 (s, 1H, CH-Ph), 6.74 (d, $J_{1,2}$ = 4.2Hz, 1H, 1-H), 7.25-7.51 (m, 15H, arom. H); 100.6 MHz ^{13}C nmr (CDCl₃): δ = 67.8 (1C, C-6), 69.6 (1C, CH), 73.0, 75.5 (2C, CH_2-Ph), 78.5, 78.9, 79.9 (3C, CH), 80.2 (1C, C-1), 101.4 (1C, CH-Ph), 126.0-129.0 (15C, C-arom.), 137.0, 137.2, 138.3 (3C, C_{ipso}); FAB-MS: 557 [M-H]+.

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