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Iodine : A Versatile Reagent in Carbohydrate Chemistry III. Efficient Activation of Glycosyl Halides in Combination with DDQ[1]

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Abstract: Iodine, either alone or in combination with DDQ, has been found to serve as a very efficient reagent for the conversion of 'disarmed' glycosyl halides into simple 1,2-*trans*-glycosides. This reagent system represents a practical alternative to traditional heavy metal promoters in glycoside synthesis.

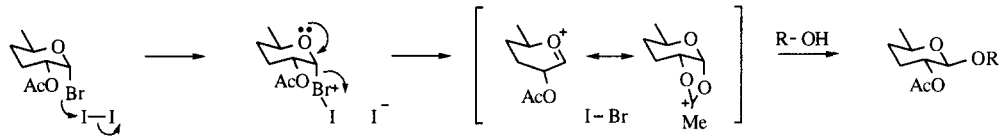
The synthesis of complex oligosaccharides remains a major challenge in organic chemistry. Since the turn of the century, numerous approaches have been explored, and procedures employing many different anomeric leaving groups have been reported.[2-4] Glycosyl chlorides and bromides have been widely studied as glycosyl donor species, with their use typically requiring mercury or silver salts as promoters,[5-10] although occasionally cadmium salts[11] have been used. To date, heavy metal salts have been the only class of activator suitable for use with peracetylated glycosyl chlorides and bromides in the synthesis of 1,2-*trans*-glycosides; the synthetic utility of such salts can be improved by use in conjunction with iodine.[12,13] In this paper we present our findings on the synthesis of simple 1,2-*trans*-glycosides using either iodine alone, or in combination with DDQ, to activate 'disarmed' glycosyl bromides and chlorides. These observations extend our earlier report on the use of iodine as a promoter for the activation of 'armed' thiomethylglycosides in 1,2-*cis*-glycoside synthesis.[1]

The methanolysis of acetobromogalactose (**1**) at room temperature in the presence of a stoichiometric amount of iodine is a fast, exothermic process that gives rise to β-methyl glycoside (**2**) (70%) plus degraded donor (Table 1, entry 1). At ice-bath temperature, the same reaction is much slower (Table 1, entries 2-3), but no degradation of donor is observed. If the reagents and reactants are mixed at ice-bath temperature in the presence of powdered 4Å molecular sieves (0.1g/ml) and then allowed to slowly warm to room temperature, a near quantitative yield of the β-glycoside is obtained (Table 1, entry 4). Use of a sub-stoichiometric amount of iodine under these conditions gives rise to a slower reaction, but a near quantitative yield of the β-glycoside is again obtained (Table 1, entry 5).

Table 1. Methanolysis of 2,3,4,6-tetra-*O*-acetyl-α-**D**-galactopyranosyl bromide (**1**) in the Presence of Iodine.

Entry No	**1**(mmol)/ MeOH	I_2 (mmol)	Time	Product (% yield)	Remarks
1	0.5 / 2 ml	0.5	5 min.	**2** (70)	Room temp.; no mol. sieves
2	0.5 / 2 ml	0.5	45 min.	**2** (70)	Ice-bath; no mol. sieves; donor recovered (25%)
3	0.5 / 2 ml	0.5	4 h.	**2** (80)	Ice-bath; no mol. sieves; donor recovered (5%)
4	0.5 / 2 ml	0.5	1 h	**2** (>95)	Ice-bath → room temp.; 4Å mol. sieves present
5	0.5 / 2 ml	0.25	3 h.	**2** (>95)	Ice-bath → room temp.; 4Å mol. sieves present

The precise mechanism of this process is not understood; it is conceivable that iodine acts as a halophile, resulting in iodobromonium ion formation, followed by fragmentation to give I-Br and a carbohydrate-derived oxocarbonium ion (Scheme 1).[14,15]



Scheme 1

Application of this activation procedure to the synthesis of other alkyl glycosides was then investigated. Of particular interest were 2-(trimethylsilyl)ethyl glycosides, which are versatile synthetic intermediates for oligosaccharide synthesis,[16,17] and hydrophobic benzyl[18] and octyl[19] glycosides, which are commonly used in biochemical studies. Results are summarised in Table 2. Treatment of donor (**1**) with 2-(trimethylsilyl)ethanol (**8**) in acetonitrile at room temperature in the presence of iodine (1.5 mol equiv) resulted in an exothermic reaction from which glycoside (**12**) was obtained in 65% yield, together with degraded donor (Table 2, entry 1). Carrying out the reaction at a lower temperature did not improve the yield (Table 2, entry 2). In contrast, the more reactive acceptor benzyl alcohol (**9**) reacted smoothly with donor (**1**) to give acetylated benzyl galactoside (**13**) in excellent yield (Table 2, entry 3).

In an attempt to overcome the problematic exothermic nature of the iodine-promoted glycosyl bromide activation procedure, we looked to other reagents that might moderate the reactivity of this system. We noted that thioglycosides can be activated by both ionic and radical processes, by employing either iodonium ion-releasing agents,[20] electrochemical conditions[21,22] or single electron transfer agents,[21] respectively. In light of the versatile oxidation chemistry accessible with DDQ,[23] we were drawn to investigate the effect of DDQ on glycosyl halide activation.

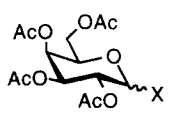
DDQ alone did not activate donor (**1**) (Table 2, entry 4). However, iodine and DDQ together proved to be a very effective combination for the activation of this donor, and although the reaction rate was dependent on the concentration of both of these reagents, use of sub-stoichiometric quantities of both iodine and DDQ together still gave rise to efficient glycosylation of acceptor (**8**) (Table 2, entries 5-10). The difficulties encountered due to the exothermic nature of the reaction obtained with iodine as the sole promoter were eliminated, and the iodine / DDQ system could be used successfully at room temperature, giving high yields of the desired products. In fact, crude products were practically pure 1,2-*trans*-glycoside, as judged by NMR spectroscopy.

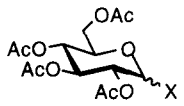
Whilst acetonitrile proved to be the most effective solvent for carrying out this type of reaction, both 1,4-dioxan and dichloromethane could be used with equivalent overall yield, but longer reaction times were necessary (Table 2, entries 5,11,12). Donor (**1**) reacted efficiently with acceptors (**8**), (**9**) and (**10**) in the presence of iodine / DDQ to give the corresponding glycosides (**12**), (**13**) and (**14**), respectively, in near quantitative yield (Table 2, entries 10,13,14). Whilst the reaction generally benefitted from the presence of 4Å molecular sieves (3Å sieves were less effective), which may trap any H-I produced in addition to removing moisture, reaction rates were typically slower (compare Table 2, entries 13, 15). The activation process described is not specific to *galacto*-configured donors, and a variety of other glycosyl halides could be converted to the corresponding glycosides in excellent yield (Table 2, entries 16-24).

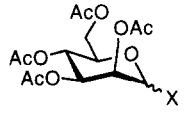
Table 2.[a] Glycosylation of Simple Alcohols Using Glycosyl Halide Donors in the Presence of $I_2 \pm$ DDQ.[b,c]

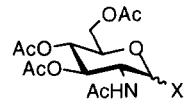
Entry No	Donor	Acceptor	I_2 (mol equiv)	DDQ (mol equiv)	Time (% yield)	Product	Remarks
1	**1**	**8**	1.5	--	25 min.	**12** (65)	Ice-bath temp.
2	**1**	**8**	1.5	--	5 h.	**12** (65)	-20°C
3	**1**	**9**	1.5	--	90 min.	**13** (>90)	Ice-bath → room temp.
4	**1**	**8**	--	1.5	no reaction		
5	**1**	**8**	1.5	1.5	45 min.	**12** (>90)	
6	**1**	**8**	1.5	0.75	3.5 h.	**12** (>90)	
7	**1**	**8**	1.5	0.38	4 h.	**12** (>90)	
8	**1**	**8**	1.0	1.0	4h.	**12** (>90)	
9	**1**	**8**	0.5	1.0	36h.	**12** (>90)	
10	**1**	**8**	1.0	0.5	3 h.	**12** (>90)	
11	**1**	**8**	1.5	1.5	7 h.	**12** (>90)	in 1,4-dioxan
12	**1**	**8**	1.5	1.5	2 h.	**12** (>90)	in dichloromethane
13	**1**	**9**	0.5	0.25	30 min.	**13** (>90)	
14	**1**	**10**	1.0	0.5	30 min.	**14** (>90)	
15	**1**	**9**	0.5	0.25	10 min.	**13** (80)	no mol. sieves
16	**3**	**8**	1.5	1.5	5.5 h.	**15** (>90)	
17	**4**	**9**	1.0	0.5	15min.	**16** (>90)	
18	**4**	**9**	1.0	--	30min.	**16** (80)	Ice-bath → room temp.
19	**4**	**10**	1.0	0.5	30 min.	**17** (>90)	
20	**5**	**10**	1.5	1.5	12 h.	**18** (>90)	
21	**6**	**8**	1.5	1.5	3.5 h.	**19** (60)	Ice-bath → room temp.
22	**7**	**11**	1.5	1.5	2 h.	**20** (85)	in *i*PrOH
23	**7**	**8**	1.5	1.5	<1h	**21** (80)	α/β 4:1
24	**7**	**8**	1.5	1.5	<1h	**21** (>90)	α/β >97:3[d]

[a] Reactions were carried out at room temp. (approx. 20°C.) with donor (0.25-1 mmol) and acceptor (2.5 mol equiv) in MeCN (1ml/0.1g of donor) containing powdered 4Å molecular sieves (0.1g/ml), unless otherwise indicated. [b] Ceric ammonium nitrate proved less effective than DDQ. [c] Similar yields were obtained when the reactions detailed in entries 8 and 20 were conducted on a 5g+ scale. [d] Conducted in $MeCN/CH_2Cl_2$ (2:3) at -18°C (5h)→5°C (12h).



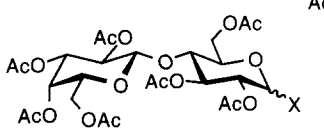




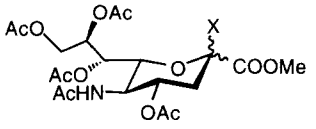


1 X = α-Br; **2** X = β-OMe; **3** X = α-Br; **15** X = β-OSE; **4** X = α-Br; **16** X = β-OBn; **5** X = α-Cl; **18** X = β-OOct
12 X = β-OSE; **13** X = β-OBn **17** X = β-OOct
14 X = β-OOct

8 $Me_3SiCH_2CH_2OH$ (SEOH)
9 BnOH
10 Octan-1-ol
11 *i*PrOH



6 X = α-Br; **19** X = β-OSE;



7 X = β-Cl
20 X = α-*i*Pr
21 X = α/β-OSE

Less reactive glycosyl halides, such as (**6**), did not react well with (**8**) in the presence of iodine alone (not shown) and addition of DDQ was necessary for the reaction to take place (Table 2, entry 21). The yield, though comparable to the Koenigs-Knorr reactions, was lower than those obtained with the more reactive glycosyl

halides described above. The usefulness of the present methodology is further exemplified by the synthesis of the sialic acid derivatives (**20**) and (**21**). In the presence of iodine / DDQ, acetochlorosialic acid (**7**) reacted smoothly in isopropanol affording (**19**) in very good yield, with complete α-stereocontrol (Table 2, entry 22). The corresponding reaction with acceptor (**8**) in acetonitrile gave a 4:1 α/β-mixture of (**21**) in good yield at room temperature (Table 2, entry 23). When the reaction was carried out in a mixture of acetonitrile and dichloromethane at lower temperature, an improved yield and almost complete α-stereocontrol was obtained (Table 2, entry 24).

Clearly iodine, either alone or in combination with DDQ, serves as an effective activator of 'disarmed' glycosyl chlorides and bromides in the synthesis of 1,2-*trans*-glycosides on a 100mg-5g scale. The activation of 'disarmed' thioglycosides under similar conditions is currently under investigation. The observations reported herein are complemetary to those recently reported by this laboratory for the use of iodine as an activator of 'armed' thioglycosides in 1,2-*cis*-glycoside synthesis.[1] Whilst the mechanisms of the iodine ± DDQ activaton processes remain to be established, these procedures represent practical alternatives to traditional Koenigs-Knorr-type reactions for the synthesis of simple alkyl glycosides.

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