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Glycosylation Chemistry Promoted by Iodine Monobromide : Efficient Synthesis of Glycosyl Bromides from Thioglycosides, and *O*-Glycosides from 'Disarmed' Thioglycosides and Glycosyl Bromides[1]

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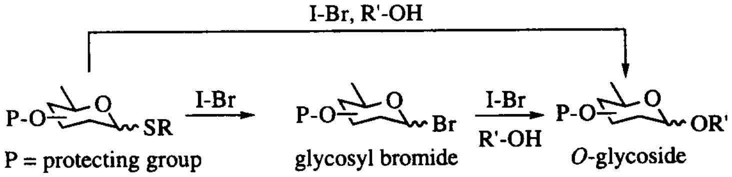
Abstract: Iodine monobromide has been found to be an efficient reagent for the conversion of both 'armed' and 'disarmed' thioglycosides (-SMe, $-SPr^i$, -SPh) into glycosyl bromides. This reagent is compatible with most common protecting groups, and *O*-glycosidic linkages. The additional potency of I-Br, compared to iodine, as an iodonium ion source also permits the glycosylation of sugar alcohols by 'disarmed' glycosyl bromides and thioglycosides. © 1997 Elsevier Science Ltd.

In connection with studies on the reactivity of sugar building blocks, we had need of a series of variously protected glycosyl donors bearing thioalkyl, thioaryl and halide leaving groups. For this study thioglycosides were attractive precursors to glycosyl halides since such compounds are sufficiently stable to allow protecting group manipulations, but are also convertible to the anomeric halides.[2] Typical reagents for effecting halide formation include Br_2 / Cl_2,[3] Br_2CHOCH_3 / Cl_2CHOCH_3,[4] and $CuBr_2$-Bu_4NBr.[5] The conversion of thio- and seleno-glycosides to glycosyl fluorides has received attention,[6] as has the generation of glycosyl halides from hemiacetals,[7] glycosyl acetates[8] and *O*-alkyl glycosides.[4] We note several examples in the recent literature where thioglycosides prove to be ineffective donors in glycosylation reactions either during direct activation[9] or during conversion to a glycosyl halide for subsequent activation.[10] It would appear that in some cases the traditional two-step activation of thioglycosides[3] (*i.e.* conversion to a glycosyl halide, followed by activation in the presence of an alcohol) is still a valuable method.

We have recently demonstrated the use of iodine as an efficient activator of 'armed' thioglycosides in oligosaccharide synthesis and 'disarmed' glycosyl halides in the synthesis of simple alkyl glycosides.[11,12] We therefore sought more powerful iodine-based activators capable of effecting disaccharide synthesis from 'disarmed' thioglycosides and glycosyl halides. In light of the established greater potency of I-Br than I-I as an iodonium ion source,[13] we reasoned that it should be possible to activate 'disarmed' thioglycosides with I-Br (Scheme 1).



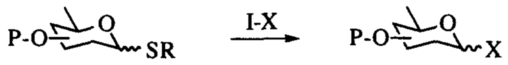
Scheme 1: Proposed Activation of Thioglycosides with I-Br

Our expectation was that in the absence of an acceptor alcohol glycosyl bromides would be produced. Moreover, we felt that the additional reactivity of I-Br might permit the direct glycosylation of relatively unreactive sugar alcohols by 'disarmed' thioglycosides and also indirect coupling of these reagents by way of the corresponding 'disarmed' glycosyl bromide (Scheme 1).

Glycosyl halide formation

Initial studies with acetylated thiogalactosides proved encouraging (Table 1). Reaction of methyl tetra-*O*-acetyl-1-thio-β-**D**-galactoside (**1**) with I-Br in dichloromethane at ice-bath temperature produced the α-bromide (**2**α) in quantitative yield following an aqueous work-up. Likewise, the less reactive thioisopropyl and thiophenyl glycosides, (**3**) and (**4**) respectively, also gave the α-bromide (**2**α) in quantitative yield. In all three cases the halide (**2**α) was the sole carbohydrate product formed, as judged by t.l.c., ^{1}H and ^{13}C NMR spectroscopy.

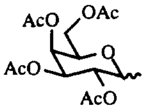
Table 1: Reaction of Thioglycosides with Iodine Monohalides[a,b]



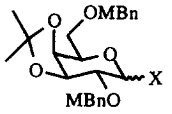
P = protecting group

Donor	R	X	Product	Solvent	Time	Temp.	α : β
1	Me	Br	**2**	DCM	10min.	ice-bath	1 : 0
3	Pr^i	Br	**2**	DCM	10min.	ice-bath	1 : 0
4	Ph	Br	**2**	DCM	10min.	ice-bath	1 : 0
5[c]	Me	Br	**6**	DCM	10min.	-10°C	1 : 0
7	Me	Br	**8**	DCM	10min.	-10°C	1 : 0
9	Me	Br	**10**	DCM	10min.	-10°C	1 : 0
11	Me	Br	**10**	DCM	10min.	-10°C	1 : 0
12	Me	Br	**13**	DCM	15min.	ice-bath	1 : 10
14	Me	Br	**15**	DCM	10min.	ice-bath	1 : 0
1	Me	Cl	**16**	DCM	10min.	ice-bath	1 : 5
17	Me	Cl	**18**	DCM	10min.	ice-bath	0 : 1

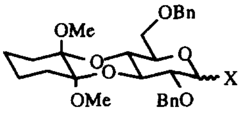
[a] Reaction carried out with 0.25 mmol of the thioglycoside and 1-1.1 mol equiv. of I-X in 2 ml of solvent;
[b] Satisfactory spectroscopic data was obtained for all glycosyl halides produced in this study; [c] MBn = 4-methoxybenzyl.



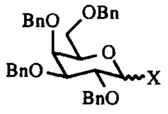
(**1**) X = β-SMe, (**2**) X = Br
(**3**) X = β-SPr^i, (**4**) X = β-SPh,
(**16**) X = Cl, (**27**) X = β-OMe



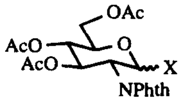
(**5**) X = β-SMe, (**6**) X = Br



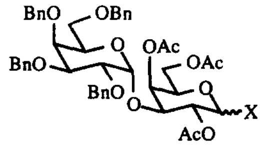
(**7**) X = α-SEt, (**8**) X = Br



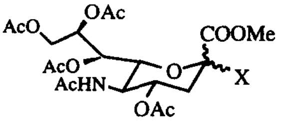
(**9**) X = β-SMe, (**10**) X = Br
(**11**) X = α-SMe



(**12**) X = β-SMe, (**13**) X = Br



(**14**) X = β-SMe, (**15**) X = Br



(**17**) X = α-SMe, (**18**) X = β-Cl

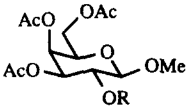
The simplicity of the thioglycoside / I-Br reaction prompted us to look at the compatibility of I-Br with a variety of commonly used protecting groups. Compounds containing isopropylidene and cyclohexane-1,2-diacetals

[(**5**),[14] (**7**)[15]], 4-methoxybenzyl and benzyl ethers [(**5**), (**7**), (**9**), (**11**)], and phthalimido groups [(**12**)] were of particular interest, as were compounds containing an inter-sugar glycosidic linkage [(**14**)[11]]. As can be seen in Table 1, all of these groups survive reaction of thioglycosides with I-Br, and glycosyl bromides are obtained in quantitative yields, thus demonstrating the feasibility of this reagent system for transformations in oligosaccharide synthesis. Pure α-bromides were obtained in all the cases except in the reaction of (**12**) with IBr where a mixture of α- and β-glycosyl bromides (**13**) was obtained. Formation of (**13β**) in the conversion of the respective glycosyl acetate to the bromide is well documented.[16]

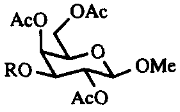
Although I-Cl is a more potent iodonium ion source than I-Br,[13] preliminary studies indicate that activation of thioglycosides, such as compound (**1**), with I-Cl gives anomeric mixtures of glycosyl chlorides (**16**) (Table 1). This is presumably a result of slow epimerisation of the kinetically-favoured β-halide product. However, the stereoselective formation of the β-chloride (**18**) from the α-thiosialoside (**17**) could be effected with I-Cl in quantitative yield.

Disaccharide synthesis

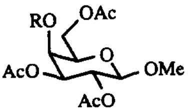
The limitation of iodine as a promoter in glycoside synthesis, either alone or in conjunction with DDQ, is the inability to bring about efficient coupling of 'disarmed' glycosyl halides and thioglycosides with secondary sugar alcohols. Reaction of 'disarmed' glycosyl bromide (**2α**) with primary sugar alcohol (**22**) gave disaccharide (**26**) after 16 hours (73% yield) with iodine as the promoter, and 1.5 hours (82% yield) on activation with iodine + DDQ. However, under similar conditions reaction with secondary sugar alcohols (**20**) and (**21**) was impractically slow. We now report that activation of 'disarmed' glycosyl bromide (**2α**) with I-Br in the presence of sugar alcohols (**19**) to (**22**) results in the formation of the corresponding 1,2-, 1,3- 1,4- and 1,6-β-linked disaccharides (**23**) to (**26**) in 73%, 50%, 35% and 70% yields, respectively.[17] The moderate yields obtained in the formation of the 1,3- and 1,4-β-linked disaccharides (**24**) and (**25**) is due mainly to acetyl group migration in acceptors (**20**) and (**21**) under the reaction conditions, and to the formation of methyl 2,3,4,6-tetra-*O*-acetyl-β-**D**-galactopyranoside (**27**) as a side product. The addition of a base, such as DABCO, to the reaction mixture was found to be advantageous in suppressing these side reactions.[19] Attempts to glycosylate acceptor (**21**) with acetobromogalactose in the presence of silver carbonate / silver perchlorate likewise gave rise to a poor yield of β-1,4-linked disaccharide (**25**) (<20% yield), together with products arising from acetate migration. The poor yield of (**25**) obtained with IBr as promoter is therefore principally due to problems with the acceptor (**21**) rather than the promoter.



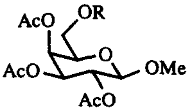
(**19**) R = H, (**27**) R = Ac
(**23**) R = (**Ac$_4$Gal**)



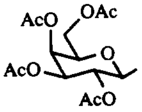
(**20**) R = H,
(**24**) R = (**Ac$_4$Gal**)



(**21**) R = H,
(**25**) R = (**Ac$_4$Gal**)



(**22**) R = H,
(**26**) R = (**Ac$_4$Gal**)



(**Ac$_4$Gal**)

In light of the faster activation of acetobromogalactose (**2α**) with IBr than with either iodine alone or in combination with DDQ, we attempted the methanolysis of thioglycoside (**1**) with IBr (iodine ± DDQ is unable to efficiently promote this reaction). The reaction in acetonitrile was complete in 15 minutes at ice-bath temperature, and methyl 2,3,4,6-tetra-*O*-acetyl-β-**D**-galactopyranoside (**27**) was the sole carbohydrate-derived product as judged by t.l.c. and ^{1}H NMR spectroscopy. Likewise, reaction of thioglycoside (**1**) with primary sugar alcohol (**22**) in the presence of IBr in acetonitrile gave the β-linked disaccharide (**26**) in 65% yield (unoptimised) in 10 minutes at ice-bath temperature. The examples given thus demonstrate the utility of IBr as a promoter for the activation of 'disarmed' thioglycosides as well as glycosyl halides.

In summary, iodine monobromide is an efficient and easy to handle reagent for the conversion of thioglycosides of varying reactivity to glycosyl bromides, and is compatible with many of the commonly used protecting groups. In addition, iodine monobromide promotes glycosylation of primary and secondary sugar alcohols by 'disarmed' glycosyl halides and thioglycosides. The differential reactivity and compatibility of I_2 / I_2+DDQ / IBr suggests scope for employing these reagents in one-pot multiple glycosylation procedures.[20]

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