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Iodine : A Versatile Reagent in Carbohydrate Chemistry II. Efficient Chemospecific Activation of Thiomethylglycosides[1]

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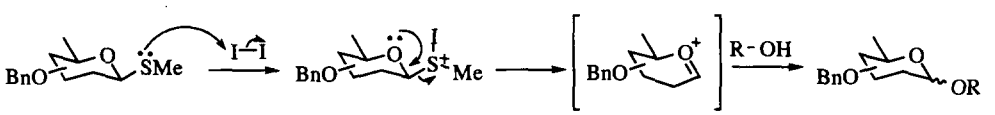
Abstract: Iodine has been found to be an efficient promoter in the alcoholysis of unprotected or fully benzylated methyl 1-thio-β-D-galactopyranoside. Stereoselective formation of 1,2-*cis* linkages in oligosaccharide synthesis using "armed" thiomethyl glycosides as glycosyl donors was also observed. Protecting groups such as acetate, benzoate, benzylidene, isopropylidene, trimethylsilylethyl *etc* are stable under the reaction conditions. Copyright © 1996 Elsevier Science Ltd

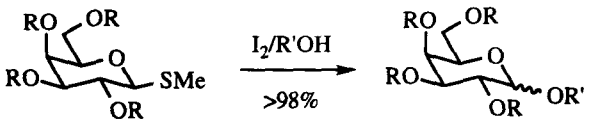
Owing to their stability under a wide variety of conditions encountered in synthetic carbohydrate chemistry, thioglycosides have found extensive use as glycosyl donors in both stepwise and blockwise synthesis of complex oligosaccharides.[2-5] A variety of reagents such as bromine followed by silver triflate or mercuric cyanide,[4] methyl triflate,[6] dimethyl(methylthio)sulfonium triflate (DMTST),[7] iodonium dicollidine perchlorate (IDCP),[8] N-iodosuccinimide (NIS)/triflic acid,[9,10] and NIS/silver triflate[9] are currently in use as promoters in glycosylation reactions using thioglycosides as glycosyl donors. Most of these reagents[2] are either corrosive, carcinogenic, explosive, produce an unbearable stench, or are light sensitive. They are all sensitive to moisture and are expensive. Alternative cheap and easy-to-handle reagents would therefore be welcome.

Among the aforementioned promoters, IDCP and NIS are perhaps the most widely used.[2] They release iodonium ion *in situ* which when attacked by a sulfur-based nucleophile forms the respective sulfonium ion which rapidly fragments to give an oxocarbonium ion and methylsulphenyl iodide.[9] We reasoned that in an "armed"[11] thiomethyl glycoside the nucleophilicity of the sulfur atom should be sufficient to result in its attack on a molecule of molecular iodine directly, resulting in release of iodide and oxocarbonium ion formation.[12] In the presence of an alcohol one might expect this to lead to the formation of a new glycosidic bond (Scheme I).[13]



Scheme I

Indeed, it was found that when methyl 1-thio-β-D-galactopyranoside **1** (*unprotected*) was stirred in methanol in the presence of iodine, the sugar slowly dissolved and in the process methanolysis of the thiomethyl group took place; methyl D-galactopyranoside **2a** (α:β, 10:1) was obtained in near quantitative yield (Table I, entry 1). The rate of reaction was dependent on iodine concentration (Table I, entries 1, 3, 5), and stoichiometric amounts of iodine were needed for the reaction to be complete in a reasonable time period (<24h) and to therefore be of practical value. When extended to more hindered alcohols such as *i*-propanol and *t*-butanol, alcoholysis



1 R = H **5** R = Bn

2 R' = Me; **3** R = *i*-Pr; **4** R'= *t*-Bu
a R = H; **b** R = Bn

Table I. Alcoholysis[a] of Methyl 1-thio-β-galactoside **1** and Methyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-galactoside **5**

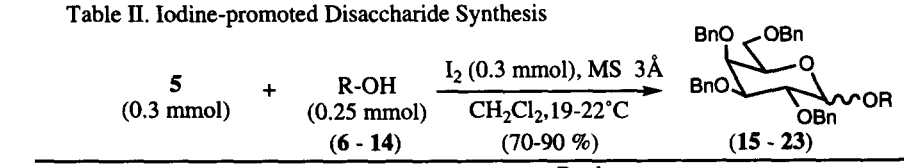
Entry No	Alcohol	I_2 (mol/mol)	Donor	Time	Product (% yield)	α:β[b]
1	MeOH	1.5	**1**	2 h.	**2a** (>98)	10:1
2	MeOH	1.5	**5**	50 min.	**2b** (>98)	1:0
3	MeOH	1.0	**1**	12 h.	**2a** (>98)	9.7:1
4	MeOH	1.0	**5**	1 h.[c]	**2b** (>90)	1:0
5	MeOH	0.5	**1**	4 days	**2a** (>98)	9:1
6	*i*-PrOH[d]	1.5	**1**	4 h.	**3a** (>98)	10:1
7	*t*-BuOH[e]	1.5	**1**	90 min.	**4a** (>98)	3:1
8	*t*-BuOH[d]	2.0	**5**	30 min.	**4b** (>98)	1.8:1

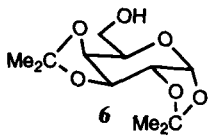
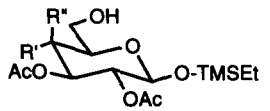
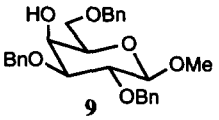
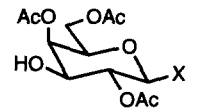
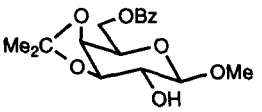
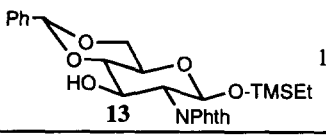
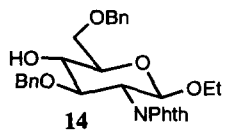
[a]0.5 mmol of **1/5** in 2 ml alcohol at 18-20°C. [b]Ratio as determined from NMR spectra. [c]Reaction did not go to completion on continued stirring (12h). [d]10 ml of the alcohols were used. [e]10 ml alcohol at 35°C.

proceeded smoothly and the respective glycosides were again obtained in near quantitative yield (Table 1, entries 6, 7). The only limitation observed in these latter reactions was the poor solubility of the thiomethyl glycoside requiring the reaction to be conducted in larger volumes of the alcohol, and in the case of the high melting *t*-butanol at slightly elevated temperatures (30-35°C). As expected, benzylated thioglycoside **5** solvolyzed even faster than **1** and *O*-glycosides were obtained in near quantitative yield (Table 1, entries 2, 4, 8). With **5** which was also insoluble in *t*-butanol, the reaction time could be considerably reduced by carrying out the reaction in the presence of dichloromethane without affecting the yield (data not shown).

Encouraged by these observations we explored the applicability of the method to oligosaccharide synthesis. There were technical problems in using the completely unprotected galactoside **1** as donor due to its limited solubility in organic solvents. The benzylated derivative **5** was therefore employed in all the subsequent experiments; results are shown in Table II. For reactions employing sugar acceptors, addition of anhydrous potassium carbonate (which presumably neutralises any HI formed) proved advantageous. The synthesis of the 4 regioisomers of galobiose proceeded in good to excellent yield (Table II, entries 1-4). The stereochemical outcome of the reaction was dependent on the regioisomer being formed, and could be influenced by the nature of the protecting groups present in the acceptor (Table II, entries 1, 2). In general, stereocontrol was modest, although absolute α-control was observed in the formation of α-1,3-galobiosides **19** and **20**. Formation of 1,3- and 1,4-linked lactosamine derivatives **22** and **23** (Table II, entries 6, 7) also proceeded in good yield and with modest stereocontrol. It is interesting to note that acetylated thioglycoside **11** (Table II, entry 4) is *not* activated under the reaction conditions reported here, offering scope for a further round of glycoside coupling with a

Table II. Iodine-promoted Disaccharide Synthesis



Entry No	R-OH	Reaction time	Product Yield (%)	α:β	Selected ^{1}H NMR data for **15α - 23α**, δ ppm
1	 **6**	4 h.	**15**, 92	1.2:1	**15α**: 7.2 - 7.45, m, 20H, 20 Ar-*H*; 5.03, d, 1H, $J_{1',2}$=3.5Hz, *H*-1'; 5.52, d, 1H, $J_{1,2}$=5.1Hz, *H*-1; 1.31,1.33, 1.45, 1.53, 4s, 2 C(CH_3)$_2$
2	 **7**: R' = H, R" = OAc **8**: R' = OAc, R" = H TMSEt = $CH_2CH_2SiMe_3$	3 h. 5 h.	**16**, 86 **17**, 82	2:1 2:1	**16α**: 5.43, d, 1H, $J_{3,4}$=3.2Hz, *H*-4; 5.17, dd, 1H, $J_{2,3}$=10.4Hz, *H*-2; 5.01, dd, 1H, *H*-3; 4.78, d, 1H, $J_{1',2}$=3.8 Hz, *H*-1'. **17α**: 5.18, 5.05, 2t, 2H, $J_{3,4}$=9.4Hz, *H*-3 and *H*-4; 4.95, d, 1H, $J_{1',2}$= 3.5Hz, *H*-1'; 4.48, d, 1H, $J_{1,2}$= 8.1Hz, *H*-1; 2.03, 1.99, 1.97, 3s, 3 (CH_3COO), -0.03, 9H, Si (CH_3)$_3$
3	 **9**	5 h.	**18**, 91	1.2:1	**18α**: 7.2 - 7.5, m, 35H, 35 Ar-*H* 5.06, d 1H, $J_{1',2}$= 2.0Hz, *H*-1'; 4.15 - 4.95, 10d, 2s, 14H, 7 (CH_2Ph); 4.27, d, 1H, $J_{1,2}$= 7.4Hz, *H*-1; 3.58, s, 3H, OCH_3
4	 **10**: X = $OCH_2CH_2SiMe_3$ **11**: X = SMe	5 h. 7 h.	**19**, 78 **20**, 71	1:0 1:0	**19α**: 5.45, d, 1H, $J_{3,4}$=3.0Hz, *H*-4; 5.10, d, 1H, $J_{1',2}$=3.2Hz, *H*-1'; 5.20, dd, 1H, $J_{2,3}$=9.3Hz, *H*-2; 4.32, d, 1H, $J_{1,2}$=8.0Hz, *H*-1. **20α**: 5.53, d, 1 H, $J_{3,4}$=3.0Hz, *H*-4; 5.27, t, 1 H, $J_{2,3}$= 8.8Hz, *H*-2; 5.13, d, 1 H, $J_{1',2}$=3.4Hz, *H*-1'; 4.23, d, 1 H, $J_{1,2}$=9.9Hz, *H*-1; 2.19, s, 3 H, SCH_3
5	 **12**	20 min.	**21**, 83	2:1	**21α**: 8.06- 7.42 and 7.2 - 7.41, 2xm, 25H, 25 Ar-*H*; 5.43, d, 1H, $J_{1',2}$= 3.4Hz, *H*-1'; 4.34, d, 1H, $J_{1,2}$=8.3Hz, *H*-1; 3.51, s, 3H, OCH_3; 1.30,1.37, 2s, 6H, C(CH_3)$_2$
6	 **13**	18 h.	**22**, 81	2:1	**22α**: 7.05 - 7.9, m, 29H, 29 Ar-*H*; 5.68, d, 1H, $J_{1',2}$=3.7Hz, *H*-1'; 5.47, s, 1H, C*H*Ph; 5.43, d, 1H, $J_{1,2}$= 8.5Hz, *H*-1; 4.35 - 5.0, 8d, 4 (CH_2Ph); 0.8 - 1.0, m, 2H, CH_2SiMe_3
7	 **14**	45 h.	**23**, 72 *	3:1	**23α**: 6.90 - 7.70, m, 34H, 34 Ar-*H*; 5.57, d, 1H, $J_{1',2}$=3.6Hz, *H*-1'; 5.13, d, 1H, $J_{1,2}$=8.6Hz, *H*-1; 1.02, t, 3H, CH_3

* Based on recovered acceptor; 46% based on isolated product.

more potent promoter.[2,5]

Data reported in Table II compare well with the literature for similar glycosylation reactions promoted by DMTST and IDCP or NIS/triflic acid using the corresponding "armed" thioethyl[7,8] and *O*-pentenyl[11] glucosides/galactosides as donors. Coupled with the successful survival of the most common protective groups, this clearly demonstrates the usefulness of iodine as a simple, mild promoter for glycosylation reactions employing armed thioglycoside donors. Our observations also suggest an additional dimension to tuning the reactivity of thioglycosides[2,5] by use of promoters of varying potency. Further work is in progress to improve the stereocontrol of the procedure reported herein.

Typical Procedures:

(a) *Alcoholysis*: Iodine (190 mg, 0.75 mmol) was added to a mixture of the *S*-methyl glycoside and the alcohol (e.g. **1**, 105 mg, 0.5 mmol in methanol, 2 ml, at room temperature) and stirred until TLC showed complete reaction (Table I). The reaction mixture was then diluted with methanol, stirred with Amberlite IRA-400 (OH) resin until the solution became colourless, and filtered. Concentration of the filtrate under reduced pressure usually gave crystals (e.g. **2a** containing traces of the β anomer **2b**). Recrystallization from methanol gave the pure α anomer.

(b) *Glycosylation with sugar alcohol*: Iodine (76 mg, 0.3 mmol) was added to a mixture of **5** (171 mg, 0.3 mmol), the acceptor (e.g. **6**, 65 mg, 0.25 mmol), powdered molecular sieves (3Å, 200 mg) and anhydrous potassium carbonate (42 mg, 0.3 mmol) in dichloromethane during stirring, and the stirring was continued at room temperature until the reaction was complete (Table II). After removing the solids by filtration through Celite, the solution was washed with aqueous sodium thiosulfate solution, dried (Na_2SO_4), concentrated and chromatographed (silica gel, 40 ml, dry vol.; eluent, ethyl acetate:hexanes=1:3) to yield the corresponding disaccharide. The α- and β-anomers were collected together and the ratio was determined by ^1H NMR spectroscopy. Subsequent rechromatography using the same eluent gave the pure α anomer.

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12. Due to the inherent nucleophilicity of the halide ion released, and the relative stabilty of the adducts formed, activation of thioglycosides with bromine / chlorine initially gives rise to glycosyl halides[2]. Further reaction *in situ* with acetic acid can give glycosyl acetates (Bonner, W.A.; *J. Am. Chem. Soc.*, **1948**, *70*, 3491).
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