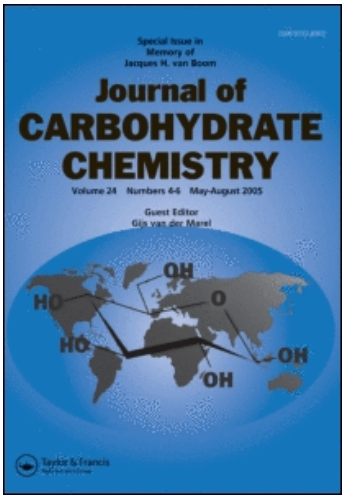

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Iodine and Its Interhalogen Compounds: Versatile Reagents in Carbohydrate Chemistry V. Synthesis of 1,2-*trans*-Linked 1-Thioglycosides from the Per-*O*-acetylated Glycoses

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IODINE AND ITS INTERHALOGEN COMPOUNDS: VERSATILE REAGENTS IN CARBOHYDRATE CHEMISTRY V. SYNTHESIS OF 1,2-*TRANS*-LINKED 1-THIOGLYCOSIDES FROM THE PER-*O*-ACETYLATED GLYCOSES[1,2]

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ABSTRACT

Treatment of per-*O*-acetylated mono- and di-saccharides with (alkyl/arylthio)trimethylsilane and iodine at ambient temperature results in the formation of the corresponding 1,2-*trans*-1-thioglycosides in very high yield. In the case of higher boiling thiols such as ethanethiol, the reaction can be effectively carried out in the presence of the thiol itself instead of the silylated derivative, but the reaction is not stereospecific. Moreover, in the latter reactions a portion of the starting material remains unchanged even on prolonged reaction. With β-D-glucose pentaacetate (**11**) as the starting material, its epimerisation occurred during the reaction and therefore the recovered starting material was of α-D-configuration. In addition, the methyl disulphide-hexamethyldisilane system has been found to serve as an effective and cheaper alternative to the expensive (methylthio)-trimethylsilane.

INTRODUCTION

Thioglycosides serve as valuable intermediates in synthetic carbohydrate chemistry.[3] Most commonly they are synthesized from the respective per-*O*-acetylated derivatives and the desired thiol or, more recently, its trimethylsilyl (TMS) derivative in the presence of a Lewis acid catalyst such as BF_3, ZnI_2 or TMS triflate.[4] Use of the TMS derivative of the thiol has been considered advantageous in that the decreased nucleophilicity of the sulfur atom in the silyl derivative, as compared with the free thiol, helps minimise complicating

side reactions, such as acid catalyzed epimerization of the initially formed 1,2-*trans*-1-thioglycoside and introduction of additional thiol-derived residue(s) on to the sugar moiety. This significantly improves the yield and stereoselectivity of the reaction.[4] The silylated thiol also has the distinct advantage of being considerably less odourous than its thiol precursor. In light of our recent observations on the strong Lewis acid-like behaviour of iodine in acyl transfer reactions,[2] and its interaction with silylated alkyl/aryl thio/seleno alcohols as noted by others,[5-7] we decided to investigate the feasibility of using iodine as a cheap and easy to handle substitute for the highly moisture sensitive reagents mentioned above.

RESULTS AND DISCUSSION

First, we wanted to ascertain the potential of iodine for the cleavage of the Si-S bond in (methylthio)trimethylsilane (**1**). During the course of studies on the *in situ* generation of TMS-I from (phenylseleno)trimethylsilane and iodine, and the insertion of selenium into carbonyl compounds,[5] Detty has noted that **1** failed to react with iodine under similar conditions and attributed the difference in reactivity of **1** to the stronger Si-S bond as compared with the Si-Se bond. On the other hand Evans and coworkers[6,7] observed that thioketalization proceeds under extremely mild conditions when carbonyl compounds are treated with **1**. Presence of any Lewis acid as minor impurity in **1** was sufficient to cause the reaction. In our own hands, when a solution of **1** in acetonitrile was titrated against a solution of iodine (1 mol equiv) in acetonitrile (added by syringe) decolourisation of the iodine colour occurred in the initial stages of titration and a brown solution was obtained at the end of the addition of the iodine solution. This is suggestive of complete consumption of iodine on reaction with **1**. Clearly these latter results are at variance with the observations noted by Detty.[5] Intrigued by this apparent discrepancy we probed the reaction of **1** with iodine in deuteriochloroform by NMR spectroscopy. Results are shown in Table 1. The downfield shift of the methyl signals observed in the NMR spectrum is in accordance with the reactions shown in Scheme 1. The signal appearing at δ 2.43 for the thiomethyl protons is indicative of the dimerization of the initially formed methyl sulfenyl iodide and is hardly surprising considering the weak nature of the I-S bond in methyl sulphenyl iodide (ca. 49.3 kcal/mol[8]). The chemical shift observed is in agreement with the values reported for the methyl protons in MeS-SMe .[9]

Reactions using (alkyl/arylthio)trimethylsilanes:

Considering the excellent oxygenophilicity of silicon and from the published data[10] on the ease of ester cleavage by TMS-I, reaction of per-*O*-acetylated carbohydrates with **1** in the presence of iodine as shown in Scheme 2 could then be rationalised. The strength of

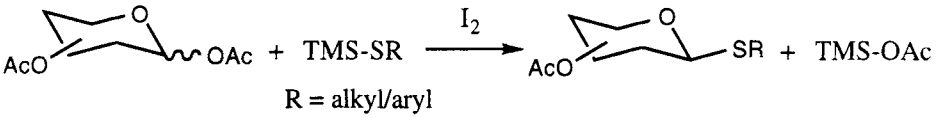
Table 1. Effect of Iodine on the NMR Chemical Shifts[a] of **1** in $CDCl_3$.

Description	^1H NMR (δ)		^{13}C NMR (δ)	
	$(CH_3)_3Si$	CH_3S	$(CH_3)_3Si$	CH_3S
Before adding I_2	0.29	1.97	0.20	8.12
After adding I_2[b]	0.79[c]	2.43[c]	5.56[c]	22.30[c]

a. In ppm relative to δ 7.25 for the residual proton in $CDCl_3$ in the ^1H NMR spectrum and δ 77.00 for the ^{13}C in $CDCl_3$ in the ^{13}C NMR spectrum. b. 1 mol of I_2/mol of **1** was used. Spectra recorded less than 10 min after mixing. c. Same values were obtained with mol ratio of I_2:**1** = 0.5:1 and 1.5:1.

$$Me_3Si\text{-}SMe + I_2 \longrightarrow Me_3Si\text{-}I + MeS\text{-}I$$
$$2\ MeS\text{-}I \longrightarrow MeS\text{-}SMe + I_2$$
$$2\ Me_3Si\text{-}SMe + I_2 \longrightarrow 2\ Me_3Si\text{-}I + MeS\text{-}SMe$$

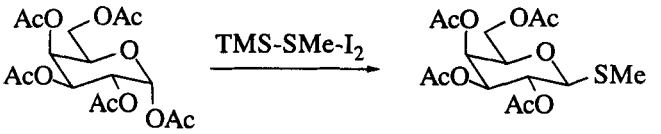
Scheme 1



Scheme 2

the Si-O bond coupled with the very low reactivity of iodine towards "disarmed" thioglycosides[11] should prevent reverse formation of the glycosyl acetate from TMS-OAc and the thioglycoside product. Indeed, by employing penta-*O*-acetyl-α-D-galactopyranose (**2**) as the model substrate (see Table 2, entry 4) reaction of 2 mol equiv of **1** and 1.5 mol equiv of iodine in acetonitrile at rt and TLC (EtOAc/hexane 2:3, v/v) carried out after 5 min it was found that most of **2** had already been consumed during that short reaction time. Following an aqueous work up and flash chromatography the crystalline product obtained (in 75% yield) was characterized as **8** by NMR on comparison with authentic sample.[4] Encouraged by this result reaction conditions were then optimised. Results are shown in Table 2. As iodine is regenerated with the formation of the thioglycoside and TMS-OAc

Table 2. Iodine-Promoted Reaction[a] of Compound **2** with TMS-SMe (**1**).



2 **8**

Entry no.	TMS-SMe (mol/mol **2**)	Iodine (mol/mol **2**)	Solvent (4 mL/mmol **2**)	Reaction time (min)	Yield of **8** (%)
1	2.0	0.25	CH_3CN	90	--[b]
2	2.0	0.25	CH_3CN	4 days	--[c]
3	2.0	0.5	CH_3CN	90	--[b]
4	2.0	1.0	CH_3CN	60	20[d]
5	2.0	1.5	CH_3CN	5	75
6	1.5	1.5	CH_3CN	<2	90
7	1.3	1.0	CH_3CN	<2	>90
8	1.2	1.0	CH_3CN	<2	>90
9	1.2	0.8	CH_3CN	<2	>90
10	1.2	1.0	CH_2Cl_2	2	90
11	1.2	1.0	Toluene	2	90
12	1.2	1.0	Dioxan	20	70
13	1.2	1.0	Ether	20	65

a Iodine was added to a solution of **2** in the desired solvent followed by **1**, except for entries 1 and 3 to 5 where addition of **1** preceded that of iodine; b Only traces of the product had been formed when the reaction was stopped after the time mentioned in the Table. Most of the starting material returned unchanged along with some **7**; c TLC revealed incomplete reaction. ^1H NMR spectrum of the product mixture showed **7**:**8**:**2** = 1:0.4:0.4; d Calculated from the ^1H NMR spectrum of the product mixture. The remaining material was composed of **7** and **2**.

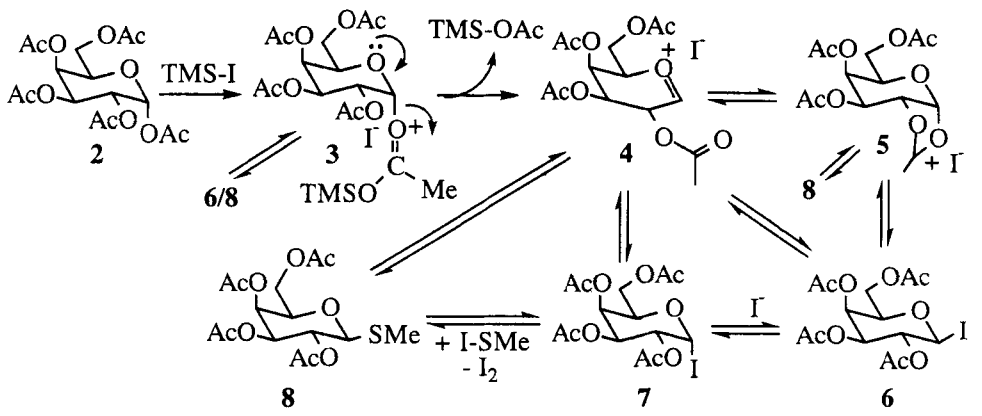
(see Scheme 1), the reaction should theoretically be catalytic with respect to iodine concentration. Although product formation was observed at low iodine concentrations (entries 1-4, Table 2) the reaction was found to be impractically slow. Thus at 25 mol% of iodine concentration (relative to **2**), considerable amount of the glycosyl acetate (**2**) remained unaffected even after 4 days of reaction at room temoerature (entry 2, Table 2). Interestingly, however, the major product of this reaction was shown to be the α-glycosyl iodide **7** by NMR. The large excess of **1**, as compared with iodine, present in the reaction mixture seemed to be responsible for the low rate of reaction, as all of the iodine added

must have been used up in the formation of the intermediate TMS-I. The reaction mixture corresponding to entries 1 and 2, Table 2, for example, was colourless, thereby showing the absence of free iodine. In contrast, excellent results were obtained when lower ratios of concentrations (of **1** and iodine) were used for the reaction (entries 5-7, Table 2). The lower yield obtained in the reaction in entry 5 (Table 2) as compared with that in entry 9 (Table 2) can be attributed to the presence of a higher concentration of TMS-I present in the former leading to the formation of some degradation products in that reaction. Per-*O*-acetylated glycoses such as **2** are unaffected by iodine and therefore best results are obtained when iodine was first added, followed by addition of **1** dropwise by syringe, after dissolution of most of the added iodine. The reaction was found to be nearly complete at the end of the addition of **1**. Traces of the α-glycosyl iodide (**7**) detected by TLC in the initial stages of the reaction were consumed in course of time leading to virtually quantitative yields of the thioglycoside. However, as epimerisation of 1,2-*trans*-1-thioglycosides is dependent upon temperature, higher temperatures or prolonged reaction times have been found to give some 1,2-*cis*-1-thioglycosides as by-products in some reactions.

Suitability of solvents other than acetonitrile for the reaction of **1** and **2** was then examined (Entries 10-13, Table 2). Chlorinated aliphatic hydrocarbons such as dichloromethane and aromatic hydrocarbons such as toluene were found to be equally acceptable. Oxygenated solvents such as diethyl ether and dioxane were, however, proved slightly inferior (see Table 2).

Based upon these observations (see also results to follow) the following mechanism involving the α-glycosyl iodide intermediate **7** derived from the oxocarbenium ion **4** via the cyclic carbonium ion **5** and the β-glycosyl iodide **6** was considered (Scheme 3). Monitoring the reactions carried out under controlled conditions[12] using the sugar derivative **2** and **1**/TMS-SEt in $CDCl_3/CD_3CN$ by NMR have indeed shown presence of **7**[13] [^{1}H NMR ($CDCl_3$) δ 7.03, d, 1H, $J_{1,2}$ = 4.2 Hz, H-1 of **7**]. Similar experiments conducted in NMR tubes using **9** and **14** as substrates have also revealed formation of the corresponding glycosyl iodide intermediates [^{1}H NMR ($CDCl_3$) δ 6.93, d, 1H, $J_{1,2}$ = 4.3 Hz, H-1 of acetoiodoglucose[13] derived from **9** and δ 6.67, d, 1H, $J_{1,2}$ = 1.5 Hz, H-1 of acetoiodomannose[13] derived from **14**].

Using acetonitrile as solvent, reaction of **1** (1.2 mol equiv) with compounds **9**, **11**, **12**, **14** and **16** was then carried out in the presence of iodine (1 mol equiv). Results are shown in Table 3. Thus formation of the respective 1,2-*trans*-linked thioglycosides (**10**, **13**, **15**, **17**) could be achieved in excellent yields (see Table 3) in short reaction times. Reaction of α- and β-glycosyl acetates **9** and **11** with **1** revealed no differential reactivity, as is often the case with the corresponding Lewis acid-promoted reactions (in which the β-



Scheme 3

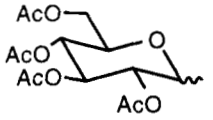
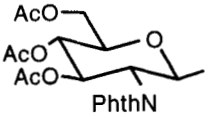
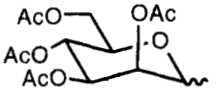
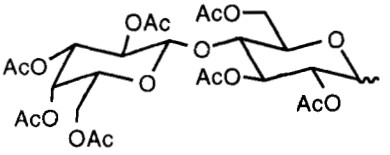
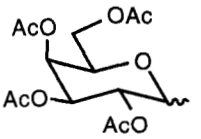
anomer shows higher reactivity over its α- epimer). Reaction of **1** with the glucosamine derivative **12** and the disaccharide derivative **16** also occurred efficiently (Table 3).

Reaction of **2** with (phenylthio)trimethylsilane was then attempted (see Table 3). Monitoring the reaction by TLC revealed complete disappearence of the starting material within about two minutes of addition of the silylated thiol. Traces of 1,2-*cis*-linked thioglycoside were also obtained in this reaction which is a consequence of epimerisation of the initially formed 1,2-*trans*-linked glycoside **18**. Prolonging the reaction results in increased formation of the 1,2-*cis*-glycoside. This phenomenon was also observed when either ethanethiol (see discussion below) or its TMS derivative was used as the source of thiolate anion.[14]

Reactions using ethanethiol:

Following the observation that the reactions of per-*O*-acetylated carbohydrates with silylated thiols could efficiently be carried out at rt we decided to investigate the reaction of ethanethiol with **2** at room temperature. Thus when a solution of **2** in acetonitrile was treated with ethanethiol, added in drops by syringe, the reaction was found to be complete (TLC, EtOAc/Hexane, 2:3) with the completion of the addition of the thiol, and the β-thioglycoside **19** could be isolated in 80% yield after column chromatography. Under these conditions the epimerisation product **20** was formed only in small amounts (less than 10%). It was also observed that traces of the starting material (**2**) remained unchanged, and could be recovered during the isolation of **19** by chromatography. Prolonged reaction also did not result in the complete disappearence of **2**. However, under such conditions epimerisation of **19** proceeded smoothly and after 24 h at room temperature the α-

Table 3. Iodine-Promoted Synthesis of Per-*O*-acetylated Thioglycosides.[a]

	Substrate	Product (Yield, %)	Sulfur reagent	Reaction time
	**9**, α-OAc	**10**, β-SMe (>90)	TMS-SMe	1.5 h
	11, β-OAc	**10**, β-SMe (>90)	TMS-SMe	1.5 h
	11, β-OAc	**21**, α-/β-SEt (65)[b]	Et-SH	10 min
	9, α-OAc[c]	**10**, β-SMe (95)	MeS-SMe-HMDS	1.5 h
	**12**, β-OAc	**13**, β-SMe (90)	TMS-SMe	15 min
	12, β-OAc	**13**, β-SMe (>95)	TMS-SMe	2 h
	**14**, α-/β-OAc	**15**, α-SMe (90)	TMS-SMe	15 min
	14, α-/β-OAc	**22**, α-/β-SEt (75)[d]	Et-SH	10 min
	**16**, α-OAc	**17**, β-SMe (70)	TMS-SMe	2 h
	**2**, α-OAc	**18**, β-SPh (80)	TMS-SPh	2 min
	2, α-OAc	**19**, β-SEt (85)	TMS-SEt	2 min at 18 °C
	2, α-OAc	**19**, β-SEt (80)	Et-SH	5 min at 18 °C
	2, α-OAc[e]	**20**, α-SEt (60)	Et-SH	24 h
	2, α-OAc[c]	**8**, β-SMe (95)	MeS-SMe-HMDS	1.5 h

a Reaction carried out in CH_3CN (10 mL/g sugar) at rt using I_2 (1 mol equiv) and the reagent (1.2 mol equiv); b α:β = 1:1.6; **9** (yield, 30%) was obtained as by-product (see text); c Reaction carried out in CH_2Cl_2 using Me_2S_2 and HMDS (0.55 mol equiv each) and I_2 (1.2 mol equiv) at rt; d α:β = 1:0.2; e Reaction carried out in CH_2Cl_2, started at ice-bath temperature and brought to rt and stirred for 24 h.

thioglycoside **20** could be isolated in 60% yield following aqueous work up and column chromatography (see Table 3). As the reaction is mildly exothermic and higher temperatures promoted epimerisation it was important that the reaction was carried out at about 18 °C, the thiol being added slowly by syringe.

Detection of unchanged starting material **2** in the above reactions led us to consider the possibility of acetate ion (released from **2** upon initial reaction) competing for the intermediate **4** formed in the reaction resulting in the reverse formation of **2**. In such an event it is reasonable to expect formation of the epimerisation product if a β-glycosyl acetate is used as the starting material for the reaction. Indeed when a solution of **11** in acetonitrile was treated with ethanethiol in the presence of iodine, **9** and **21** were obtained as products after aqueous work up and column chromatography (see Table 3). Similarly reaction of **14** also led to the recovery of some unreacted starting material after the reaction for 10 min at room temperature (Table 3).

Reactions using methyl disulphide-hexamethyldisilane:

Considering the fact that results obtained in the above reactions using the free thiol are less than satisfactory, and the fact that silylated thiol reagents such as **1** are expensive, cheaper and more efficient alternative thiol equivalents were sought. Thus when a solution of **2** in anhydrous methylene chloride was treated with the methyl disulphide-hexamethyldisilane (MDS-HMDS) system at room temperature in presence of iodine, compound **8** was obtained in 95% yield after a reaction time of 90 min (Table 3). Reaction of per-*O*-acetylated glucose (**9**) with the MDS-HMDS system likewise gave the β-thioglycoside **10**, also in very high yield. Methylene chloride proved to be a better solvent for these reactions as the use of acetonitrile led to facile epimerisation of the β-glycoside product.

In conclusion, iodine has been found to be an extremely efficient promoter in the transformation of per-*O*-acetylated glycoses to thioglycosides. Attempts to replace the expensive (methylthio)trimethylsilane (**1**) with methyl disulphide and hexamethyl disilane (which are cheaper than **1** by a factor of ca. 500 and 8 respectively on mol equiv. basis) have proved successful using **2** and **9** as substrates.

EXPERIMENTAL

General methods. All reagents (Aldrich) were used as purchased without further purification. Solvents used for reactions were dried by storing over activated molecular sieves (4Å). Reactions were monitored by TLC, which was performed with 0.2 mm Merck pre-coated silica gel 60 F_{254} aluminium sheets. Compounds were detected by dipping the TLC plates in an ethanolic solution of sulfuric acid (4-5% v/v) and heating. Sorbsil C60 40/60 A (Sorbsil Chromatography Media) was used for column chromatography. Hexane

refers to a mixture of isomeric hexanes. Melting points (uncorrected) were determined on a Gallenkamp Melting Point Apparatus. Optical rotations were recorded on an Optical Activity Ltd. AA-1000 Polarimeter at room temperature (approximately 22 to 24 °C.). ^{1}H NMR spectra were recorded at 300 MHz on a Brucker AM300 spectrometer in deuteriochloroform. Chemical shifts are expressed relative to that of the residual proton in the deuterated solvent (δ 7.25). ^{13}C NMR spectra were recorded at 75.47 MHz. Assignments of resonances are based on published data. All the compounds (**8**,[4] **10**,[4] **13**,[4] **15**,[4] **17**,[4] **18**,[4] **19**,[15] **20**,[15] **21**,[4] and **22**[15]) reported here have been reported previously and their spectral and analytical data agreed with literature values. Room temperature refers to approximately 20 to 24 °C.

Typical Procedure for the conversion of per-*O*-acetylated sugars to their corresponding 1-thioglycosides.

Method A, using the silylated thiol or the free thiol: To a solution of the per-*O*-acetylated sugar (**2**, **9**, **11**, **12**, **14**, **16**, 1 mmol) in anhydrous acetonitrile (1 mL/100 mg sugar derivative) was added iodine (253.8 mg, 1 mmol) and the mixture was stirred at the required temperature (see Tables 2 and 3) until the solids had dissolved. The thiol reagent (1.2-1.3 mmol, see Tables 2 and 3) was then added dropwise by syringe and stirred until TLC (EtOAc/hexane, 2:3 or 1:1) showed completion of the reaction. The reaction mixture was then diluted with dichloromethane and was washed successively with aqueous sodium thiosulfate solution (10%, w/v), aqueous sodium carbonate solution (10%, w/v) and water. It was then dried (Na_2SO_4), concentrated under reduced pressure to a small volume and chromatographed on a silica gel column (50-75 mL, dry volume) using EtOAc:hexane, 2:3 as the eluent. Products were typically obtained as crystals.

Method B, using methyl disulfide-hexamethyldisilane system: To a solution of the per-*O*-acetylated sugar (**2**, **9**, 390.5 mg, 1 mmol) in anhydrous dichloromethane (4 mL) were added hexamethyldisilane (113 μL, 0.55 mmol), methyl disulfide (50 μL, 0.55 mmol), and iodine (304.6 mg, 1.2 mmol)) and the mixture was stirred at room temperature until TLC showed complete disappearence of **2**, **9**. Work up of the reaction mixture and purification of the product were carried out as described above to yield (see Table 3) the product (**8**, **10**) as crystals.

ACKNOWLEDGMENTS

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12. Iodine (50.8 mg, 1 mol equiv) was dissolved in $CDCl_3/CD_3CN$ (0.8 mL) containing **2** (78.1 mg, 0.2 mmol).The dark brown solution thus obtained was cooled to about 10 °C (or below as desired) and **1**/TMS-SEt (1.2 mol equiv) was added to it. After mixing the reagents well the reaction was monitored by NMR.
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