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Streamlined Synthesis of Per-*O*-acetylated Sugars, Glycosyl Iodides, or Thioglycosides from Unprotected Reducing Sugars[1]

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Abstract: Solvent-free per-*O*-acetylation of sugars with stoichiometric acetic anhydride and catalytic iodine proceeds in high yield (90−99%) to give exclusively pyranose products as anomeric mixtures. Without workup, subsequent anomeric substitution employing iodine in the presence of hexamethyldisilane (i.e., TMS−I generated in situ) gives the corresponding glycosyl iodides in 75−95% isolated yield. Alternatively, and without workup, further treatment with dimethyl disulfide or thiol (ethanethiol or thiocresol) gives anomerically pure thioglycosides in more than 75% overall yield.

The growing realization that carbohydrates are central to a wide array of biological processes[2] has led to the search for more practical methods for their synthesis. While major advances have been made in the application of reactivity tuning,[3] based on the concept of armed and disarmed glycosylation reagents,[4] further extension to so-called "programmable" syntheses,[5] and ultimately automated oligosaccharide synthesis,[6] the need remains for efficient syntheses of appropriately protected and/or activated sugar building blocks. Per-*O*-acetylated reducing sugars,[7] the corresponding glycosyl iodides,[8] and thioglycosides[9] are frequently used as the building blocks in oligosaccharide synthesis. A practical one-pot reaction sequence providing access to such building blocks from unprotected reducing sugars would be useful.

We have previously demonstrated that iodine can serve as a promoter for sugar per-*O*-acetylation,[10] that sugar per-*O*-acetates can be converted to the corresponding glycosyl iodides by treatment with TMS−I,[11] and that sugar per-*O*-acetates can also be converted directly into thioglycosides by treatment with TMS−I in the presence of thiols.[12] In both of these latter reactions, TMS−I was generated in situ from iodine and hexamethyldisilane (HMDS).[13] Noting recent reports of iodine-promoted acetylation of simple alcohols with stoichiometric acetic anhydride[14] and $Cu(OTf)_2$-catalyzed solvent-free synthesis of acetylated sugars together with subsequent conversion to thioglycosides upon addition of boron trifluoride etherate and thiol,[7f] we were encouraged to extend studies on iodine-mediated sugar modification reactions. We now report a facile, one-pot reaction sequence from unprotected reducing sugars, employing stoichiometric reagents, minimal workup, and purification, that provides access to per-*O*-acetylated sugars, the corresponding glycosyl iodides, or thioglycosides in excellent yield and with essentially complete anomeric stereoselectivity.

Per-*O*-acetylation of D-glucose with 5.1 molar equiv of acetic anhydride (i.e., 1.02 molar equiv per hydroxyl group) and iodine (0.7 mol % with respect to the sugar) gave complete reaction within 2 h, giving only D-glucopyranosyl esters (Table 1); no trace of furanosyl products was detectable by ^{1}H NMR spectroscopy of the crude

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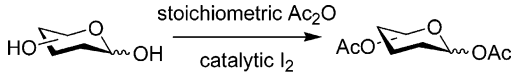
TABLE 1. Iodine-Catalyzed Solvent-Free Per-*O*-acetylation of Sugar Alcohols with Stoichiometric Acetic Anhydride and Catalytic Iodine[a]



sugar	product	time (h)	α:β	yield (%)
D-glucose	D-glucopyranose pentaacetate **1**	2	10:1	98
L-arabinose	L-arabinopyranose tetraacetate **2**	1	1:3	95
D-xylose	D-xylopyranose tetraacetate **3**	1	4:1	93
D-galactose	D-galactopyranose pentaacetate **4**	2	10:1	98
D-mannose	D-mannopyranose pentaacetate **5**	0.5	2.5:1	98
L-rhamnose monohydrate[b]	L-rhamnopyranose tetraacetate **6**	0.25	3:1	94
L-fucose	L-fucopyranose tetraacetate **7**	0.25	11:1	98
D-maltose monohydrate[b]	D-maltose octaacetate **8**	2	10:1	89
D-lactose	D-lactose octaacetate **9**	2	12:1	91
D-cellobiose	D-cellobiose octaacetate **10**	2	12:1	93

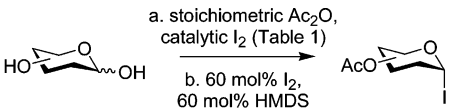
[a] With 1.02 molar equiv of Ac_2O per hydroxyl group; 0.7 mol % I_2. [b] In the case of L-rhamnose and D-maltose, an additional 1 molar equiv of acetic anhydride was necessary since these sugars are commercially available only as the monohydrates.

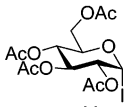
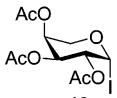
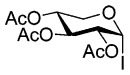
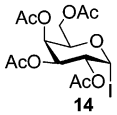
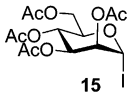
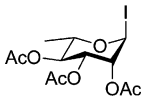
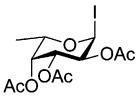
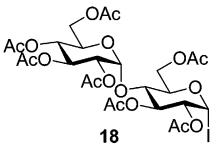
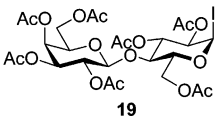
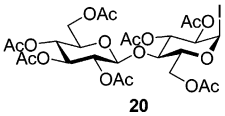
reaction product. Results for the per-*O*-acetylation of a series of pentoses, hexoses, and disaccharides are illustrated in Table 1.

With solvent-free per-*O*-acetylation in hand, we focused our attention on the formation of glycosyl iodides. In conventional per-*O*-acetylation reactions where an excess of acetic anhydride is used, neutralization followed by workup and purification is necessary. In contrast, employing stoichiometric acetic anhydride for the per-*O*-acetylation offers the possibility of a sequential reaction sequence in the same pot without further processing, as illustrated recently for $Cu(OTf)_2/BF_3{-}OEt_2$-mediated acetylation thioglycoside synthesis.[7f] Thus, per-*O*-acetylation of free sugars was conducted in the manner outlined above; after completion of the reaction (as judged by TLC), a minimum amount of dry dichloromethane (~1 mL/mmol of sugar) was added to mobilize the thick syrupy mass of the sugar per-*O*-acetate. Further addition of 0.6 molar equiv each of HMDS and of iodine resulted in the formation of the corresponding glycosyl iodides in good to excellent isolated yield within a few hours (Table 2).

Despite initial concerns about glycosyl iodide stability, all compounds described herein proved to be stable to column chromatography, and all gave satisfactory molecular ions by electrospray mass spectrometry.[15]

TABLE 2. One-Pot Conversion of Free Sugars to Per-*O*-acetylated Glycopyranosyl Iodides



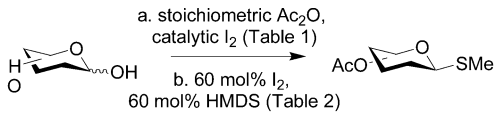
sugar	product	Time (hours)	Yield[a] (%)
D-Glucose	 **11**	6	91%
L-Arabinose	 **12**	5	75%
D-Xylose	 **13**	5	73%
D-Galactose	 **14**	3	89%
D-Mannose	 **15**	3	91%
L-Rhamnose	 **16**	1.5	88%
L-Fucose	 **17**	1.5	90%
D-Maltose	 **18**	6	82%
D-Lactose	 **19**	6	86%
D-Cellobiose	 **20**	6	90%

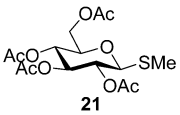
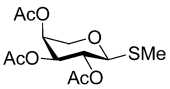
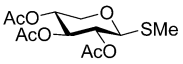
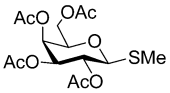
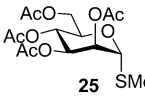
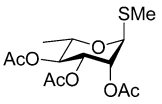
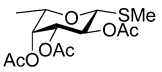
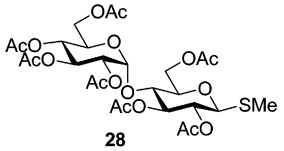
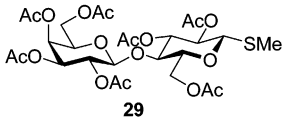
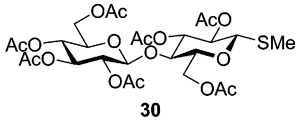
[a] Isolated yield over two steps following chromatographic purification.

One-pot synthesis of thioglycosides from unprotected sugars was then investigated. After the complete conversion of saccharides to the glycosyl iodides, as described above (and as judged by TLC), 0.6 molar equiv of dimethyl disulfide (DMDS) was added to the reaction mixture, which was stirred at room temperature for 6 h.

(15) General concern about glycosyl iodide stability is unfounded. Crystalline glycosyl iodides were first reported almost a century ago: (a) Fisher, E.; Fischer, H. *Ber.* **1910**, *43*, 2535. (b) Brauns, D. H. *J. Chem. Soc.* **1927**, *49*, 3170. In addition, the crystal structure of methyl 2,3,4-tri-*O*-pivaloyl-α-D-glucopyranosyluronate iodide has recently been reported: Bickley, J.; Cottrell, J. A.; Ferguson, J. R.; Field, R. A.; Harding, J. R.; Hughes, D. L.; Kartha, K. P. R.; Law, J. L.; Scheinmann, F.; Stachulski, A. V. *Chem. Commun.* **2003**, 1266.

TABLE 3. One-Pot Conversion of Free Sugars to Methyl Thioglycosides



sugar	product	yield[a](%)
D-Glucose	 **21**	88%
L-Arabinose	 **22**	71%
D-Xylose	 **23**	65%
D-Galactose	 **24**	83%
D-Mannose	 **25**	87%
L-Rhamnose	 **26**	81%
L-Fucose	 **27**	83%
D-Maltose	 **28**	78%
D-Lactose	 **29**	80%
D-Cellobiose	 **30**	84%

[a] Isolated yield over three steps following chromatographic purification.

TLC (CH_2Cl_2/acetone, 19/1) showed complete conversion of the iodide to a slower moving component, which was isolated and purified by flash chromatography (Table 3). All of the reactions afforded a single anomer as the sole product, a consequence of neighboring group participation.

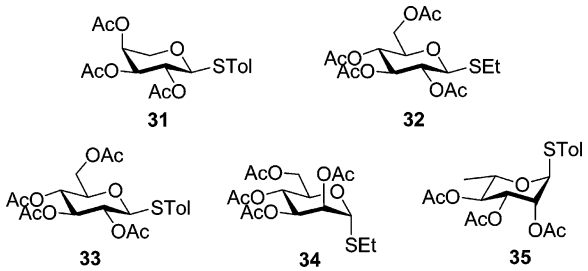


FIGURE 1. Per-*O*-acetylated ethyl and *p*-tolyl thioglycosides.

The synthesis of other thioglycosides (e.g., −SEt, −STol, etc.) was also effective when 1.2 molar equiv of the respective thiols was used instead of MeSSMe. Such reactions proceeded equally well, with complete anomeric selectivity and in very good yield (Figure 1).

In summary, iodine is a cheap and efficient catalyst for the solvent-free per-*O*-acetylation of sugars. Without workup, and with further use of iodine in conjunction with hexamethyldisilane, acetylated glycosyl iodides are afforded in excellent yield. Further still, addition of dimethyl disulfide or thiol to the same reaction mixture gives the corresponding thioglycosides with excellent anomeric stereoselectivity and very good overall yield. All of the reactions illustrated in Tables 1−3 have been carried out on a 10 mmol scale, but the procedures described are well suited for larger scale reactions; a 100 mmol scale reaction with D-glucose gave a result almost identical to those reported in Tables 1−3. This convenient, general one-pot reaction sequence minimizes reagent use, workup, and chromatography while providing flexible access to three important classes of commonly used glycosyl donor building blocks in a practical time frame.

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Supporting Information Available: ^1H and ^{13}C NMR spectra of all glycosyl iodide per-*O*-acetates and compounds **21**, **24**−**27**, and **29**−**35** are given. Literature citations are also included for the known compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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