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Convenient, in Situ Generation of Anhydrous Hydrogen Iodide for the Preparation of α-Glycosyl Iodides and Vicinal Iodohydrins and for the Catalysis of Ferrier Glycosylation

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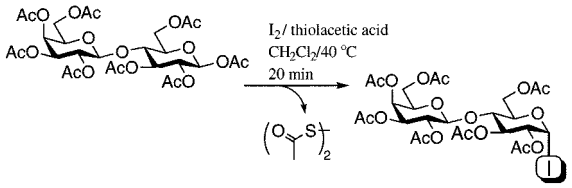
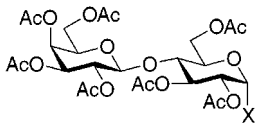
ABSTRACT



Anhydrous hydrogen iodide is generated in situ by the reaction of solid iodine and a thiol. The HI thus generated has been employed for the efficient preparation of α-glycosyl iodides and vicinal iodohydrins from the corresponding glycosyl acetates and epoxides, respectively, and for Ferrier glycosylation of alcohols and thiols.

In connection with our interest in the design and synthesis of sialyl Lewis X mimetics, the use of the per-*O*-acyl lactosyl halide **1** was required as a glycosyl donor. Given the



1a X = Br
1b X = I

enhanced reactivity of the lactosyl iodide **1b** toward nucleophilic displacement over the lactosyl bromide **1a**,[1] we were particularly interested in the efficient preparation of **1b**. While a number of reliable methods to access glycosyl iodides have been reported,[2] Gervay's recently published preparation appears to be the only one that allows for the isolation of the stereochemically pure, reportedly unstable iodides in a relatively efficient manner.[3] However, even this Gervay procedure requires the use of the expensive and highly labile reagent trimethylsilyl iodide.[3] The adaptation of the widely used method for the preparation of per-O-acetylated glycosyl bromides[4] (which entails treatment of the per-O-acetylated glycosides with anhydrous HBr in acetic acid, frequently at reflux) for the preparation of the corresponding iodides does not appear practical, due to the difficulty in obtaining anhydrous HI.[5]

(1) (a) Hashimoto, S.; Honda, T.; Ikegami, S. *Tetrahedron Lett.* **1990**, *31*, 4769−4772. (b) Schmid, U.; Waldemann, H. *Tetrahedron Lett.* **1996**, *37*, 3837−3840.

(2) (a) Ness, R. K.; Fletcher, H. G.; Hudson, C. S. *J. Am. Chem. Soc.* **1951**, *73*, 296−300. (b) Krontzer, F. K.; Schuerch, C. *Carbohydr. Res.* **1974**, *34*, 71−78. (c) Ferrari, B.; Pavia, A. A. *Carbohydr. Res.* **1980**, *79*, C1−C7. (d) Thiem, J.; Meyer, B. *Chem. Ber.* **1980**, *113*, 3075−3085. (e) Klemer, A.; Bieber, M. *Liebigs Ann. Chem.* **1984**, 1052−1055. (f) Ernst, B.; Winkler, T. *Tetrahedron Lett.* **1989**, *30*, 3081−3084. (g) Lichtenthaler, F. W.; Kläres, U.; Lergenmüller, M.; Schwidetzky, S. *Synthesis* **1992**, 179−184. (h) Paulsen, H.; Rutz, V.; Brockhausen, I. *Liebigs Ann. Chem.* **1992**, 747−758. (i) Premchandran, R. H.; Ogletree, M. L.; Fried, J. *J. Org. Chem.* **1993**, *58*, 5724−5731. (j) Lichtenthaler, F. W.; Kühler, B. *Carbohydr. Res.* **1994**, *258*, 77−85. (k) Uchiyama, T.; Hindsgaul, O. *Synlett* **1996**, 499−501. (l) Schmid, U.; Waldemann, H. *Tetrahedron Lett.* **1996**, *37*, 3837−3840. (m) Schmid, U.; Waldemann, H. *Liebigs Ann./Recl.* **1997**, 2573−2577.

(3) (a) Gervay, J.; Hadd, M. J. *J. Org. Chem.* **1997**, *62*, 6961−6967. (b) Gervay, J.; Nguyen, T. N.; Hadd, M. J. *Carbohydr. Res.* **1997**, *300*, 119−125.

(4) See, e.g.: Helferich, B.; Weis, K. *Chem. Ber.* **1956**, *89*, 314−318.

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Concurrently, in our investigations of the iodine-catalyzed Ferrier reaction,[6] it was observed that the reaction of tri-*O*-acetyl glucal and a thiol catalyzed by iodine (20 mol %) in THF resulted in the formation of the byproduct 4-iodobutan-1-ol,[7] apparently the reaction product of the solvent molecule with in situ generated HI. Investigation into this reagent mixture indicated that the source of the HI was likely the result of the oxidation of the thiol in the presence of iodine. Therefore, it was envisaged that the reaction of iodine with a thiol in an organic solvent might provide a synthetically useful source of anhydrous HI. HI thus generated could be conveniently applied to the synthesis of glycosyl iodides from per-O-acetylated glycosyl acetates and the synthetically useful vicinal iodohydrins from the corresponding epoxides and could serve as an efficient catalyst for the Ferrier glycosylation reaction.

The oxidation of thiols with iodine is the basis of well-established methods for the iodometric titration of thiol groups,[8] for the preparation of peptide disulfide linkages,[9] and for the oligomerization of dithiols.[10,11] However, it should be noted that, in all reported cases, the oxidation proceeds to a significant extent only if the HI byproduct is removed by reaction with a base or by solvation in a biphasic reaction mixture. In the general scheme (Scheme 1), a thiol molecule

Scheme 1

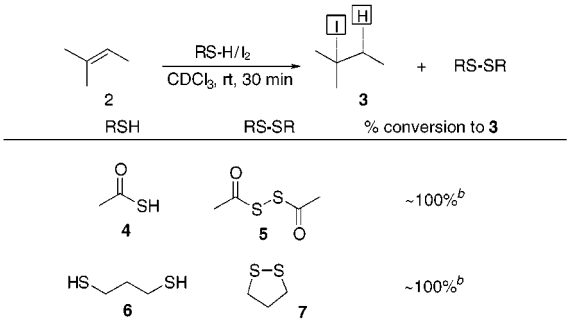
$$RSH + I_2 \longrightarrow RSI + H\text{-}I \quad (1)$$

$$RSI + RSH \longrightarrow RS\text{-}SR + H\text{-}I \quad (2)$$

reacts with molecular iodine to form an intermediate sulfenyl iodo species and one molecule of HI. The sulfenyl iodide reacts with the second thiol molecule to yield the corresponding disulfide and a second molecule of HI. While this method has been widely recognized as a route to the disulfide species, little attention has been given to its potential for the stoichiometric production of anhydrous hydrogen iodide.

In an effort to assess the efficiency for the formation of HI as the byproduct of the oxidation of thiols, the reaction of 1.0 mol equiv of thiols **4** and **6** with iodine (0.5 mol equiv) in the presence of 2-methyl-2-butene (**2**; 1 mol equiv) was monitored by ^{1}H NMR spectroscopy in $CDCl_3$. Both thiolacetic acid (**4**) and 1,3-propanedithiol (**6**) were oxidized quantitatively to their respective disulfides, and the HI adduct with 2-methyl-2-butene (**2**), 2-iodo-2-methylbutane (**3**), was produced cleanly (Table 1). Notably, an NMR signal

Table 1. Addition of HI to Alkene **2**[a] Monitored by ^{1}H NMR Spectroscopy



[a]Reaction conditions: **2** (0.245 mmol), **4** or **6** (0.245 mmol), and I_2 (0.123 mmol) were dissolved at room temperature in $CDCl_3$ (1 mL) in a 5 mm o.d. NMR tube. The reaction was monitored by ^{1}H NMR spectroscopy at 400 MHz. [b] No ^{1}H NMR signals corresponding to alkene **2** detected.

assignable to HI was not detected in either case. As expected, the same reaction of **4** or **6** in the absence of butene **2** did not produce any disulfide product, as judged by ^{1}H NMR spectroscopy.

Treatment of the per-*O*-acetyl derivatives of mono- and disaccharides with a solution of iodine (0.5 mol equiv) and thiolacetic acid (**4**; 1.0 mol equiv) in dichloromethane at reflux resulted in the rapid, highly stereoselective formation of the corresponding α-glycosyl iodides (Table 2). The crude reaction mixtures were amenable to silica gel flash column chromatography, and the products were isolated as white amorphous solids. Comparison of the reactivity of per-*O*-acetyl-*β*-D-glucose (entry 1) and per-*O*-acetyl-α-D-glucose (entry 2) reveals that the efficiency of the conversion is dependent upon the relative geometry of the anomeric acetate group and the neighboring acetate group at C-2. Presumably, in the 1,2-trans compounds, the acetate group at C-2 is likely to assist ionization of the anomeric leaving group, leading directly to a stabilized oxonium intermediate. In contrast, in the 1,2-cis systems, such ionization is not possible and a much lower yield is observed. This type of C-2 acetate group participation is well-documented for various cases of anomeric group displacement.[12] The exclusive formation of the α-iodides regardless of the configuration of the starting anomeric acetate group is a manifestation of the rapid equilibrium of the initially produced iodides that favors the thermodynamically more stable α-iodides.[3b]

In view of the 1′,2′-trans geometry at the interglycosidic linkage of lactose, the possible cleavage of the interglycosidic

(5) For the generation of anhydrous HI, see the following. (a) I_2/tetrahydronaphthalene: Hoffman, C. J. *Inorg. Synth.* **1963**, *7*, 180−182. (b) $I(py)_2BF_4/CH_2Cl_2$ + HBF_4/Et_2O; Et_3SiH: Barluenga, J.; González, J. M.; Campos, P. J.; Asensio, G. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 319−320. (c) I_2 + activated Al_2O_3/petroleum ether: Pagni, R. M.; Kabalka, G. W.; Boothe, R.; Gaetano, K.; Stewart, L. J.; Conaway, R.; Dial, C.; Gray, D.; Larson, S.; Luidhardt, T. *J. Org. Chem.* **1988**, *53*, 4477−4482. (d) $Et_2PhN{\cdot}BI_3$/AcOH: Reddy, Ch. K.; Periasamy, M. *Tetrahedron Lett.* **1990**, *31*, 1919−1920. See also: (e) Irifune, S.; Kibayashi, T.; Ishii, Y.; Ogawa, M. *Synthesis* **1988**, 366−369. (f) Brommfield, C. E. *Org. Proc. Res. Dev.* **1997**, *1*, 88−89.

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(7) Tuinman, R. J.; Koreeda, M. Unpublished results.

(8) Capozzi, G.; Modena, G. In *The Chemistry of the Thiol Group*; Patai, S., Ed.; Wiley: London, 1974; Part 2, pp 785−839.

(9) Farlow, M. W. *J. Biol. Chem.* **1948**, *176*, 71−72.

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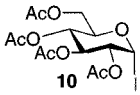
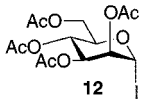
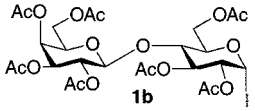
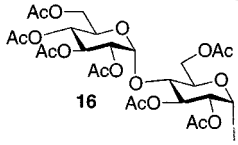
(12) Collins, P.; Ferrier, R. *Monosaccharides: The Chemistry and Their Roles in Natural Products*; Wiley: New York, 1995; pp 60−188.

Table 2. Synthesis of α-Glycosyl Iodides from Per-*O*-acetyl Sugars with in Situ Generated HI

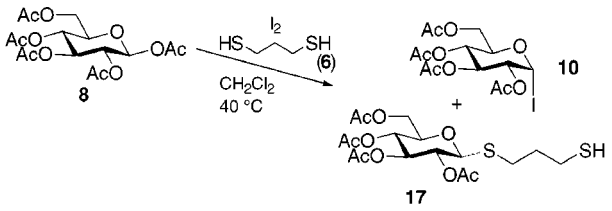
entry	substrate	product[a]	% yield[b]
1	per-*O*-acetyl-β-D-glocose (**8**)	 **10**	77
2	per-*O*-acetyl-α-D-glocose (**9**)	**10**	59
3	per-*O*-acetyl-β-D-mannose (**11**)	 **12**	76
4	per-*O*-acetyl-β-D-lactose (**13**)	 **1b**	77
5	per-*O*-acetyl-β-D-maltose (**14**)	 **16**	71
6	per-*O*-acetyl-α-D-maltose (**15**)	**16**	54

[a] δ(H-1) and $J_{1,2}$ in $CDCl_3$ (400 MHz): **10** (7.00, 4.0 Hz); **12** (6.71, 0.7 Hz); **1b** (6.92, 6.4 Hz); **16** (9.60, 4.4 Hz). [b] Yield of isolated, chromatographically pure products.

bond by HI was a concern. Thus, treatment of per-*O*-acetyl-*β*-D-lactose (**13**) with 1 equiv of HI at longer reaction times (>2 h) resulted in the formation of 2,3,4,6-tetra-*O*-acetyl-α-galactosyl iodide, albeit in low yield (<10%), and in the diminished yield of the lactosyl iodide **1b**. Interestingly, more vigorous, but brief, treatment with the reagent led to the efficient formation of the lactosyl iodide **1b**. Thus, treatment of per-*O*-acetyl-*β*-D-lactose with 2 equiv of thiolacetic acid and 1 equiv of iodine for 20 min in refluxing dichloromethane afforded, upon purification, the desired α-glycosyl iodide **1b** in 77% yield. No products of interglycosidic bond cleavage were detected in the cases of per-*O*-acetyl maltose substrates (entries 5 and 6), reflecting the lower susceptibility toward hydrolysis of the 1′,2′-cis geometry of the maltose system.

Although the efficient formation of glycosyl iodides could be achieved, with the use of the in situ generated HI, by starting from per-O-acetylated carbohydrates, those substrates such as per-N,O-acetylated 2-deoxyamino and 2-deoxy sugars did not yield their corresponding anomeric iodides even with the use of excess iodine and thiolacetic acid. While the reasons for this apparent lack of reactivity in these sugars remain unclear, in the case of 2-amino sugars, it is likely that protonation at the more basic 2-acetylamide oxygen electronically disfavors the formation of the intermediate oxonium ion or its equivalent. Although both thiols **4** and **6** proved efficient for the production of HI from iodine for addition to an alkene as described above, the use of 1,3-propanedithiol for the generation of HI for the synthesis of glycosyl iodides led to the production of the *β*-thioglycoside (**17**; Scheme 2). This thioglycoside may result from the

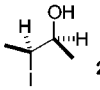
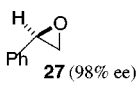
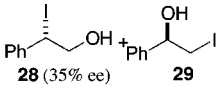
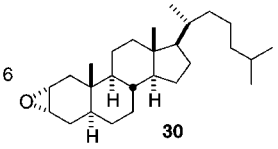
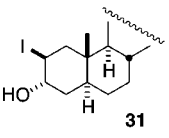
Scheme 2



nucleophilic capture of the oxonium ion intermediate or the direct displacement of the α-glycosyl iodide product.

Vicinal iodohydrins are highly versatile intermediates in synthesis.[13,14] While numerous mild methods to access such reactive intermediates exist, stereo- and regiocontrolled opening of epoxides to vicinal halohydrins continues to attract attention from synthetic chemists.[15−18] In this context, transformation of epoxides into vicinal halohydrins was examined with the use of the present in situ generated HI. As summarized in Table 3, treatment of various epoxides

Table 3. Ring Opening of Epoxides with in Situ Generated HI[a]

entry	substrate	product	% yield[b]
1	 **19**	 **20**	~100
2	 **21**	 **22**	~100
3	 **23**	 **24**	~100
4	 **25**	 **26**	~100
5	 **27** (98% ee)	 **28** (35% ee) + **29**	88 (**28**) 10 (**29**)
6	 **30**	 **31**	80

[a] Reaction conditions: epoxide compound (1 mol equiv) stirred with I_2 (0.5 mol equiv) and thiolacetic acid (**4**; 1 mol equiv) in CH_2Cl_2 at room temperature for 20 min. [b] Yield of isolated, chromatographically pure products.

with the HI resulted in the stereospecific formation of the corresponding vicinal iodohydrins in nearly quantitative yield with the exception of the case of styrene oxide (**27**). The

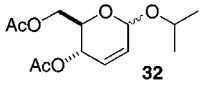
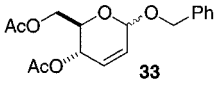
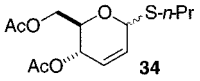
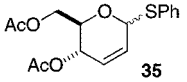
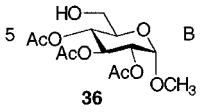
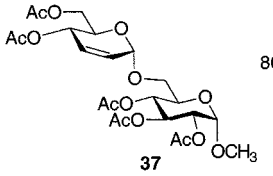
(13) (a) Maruda, H.; Takase, K.; Nishio, M.; Hasegawa, A.; Nishiyama, Y.; Ishii, Y. *J. Org. Chem.* **1994**, *58*, 5550−5555 and references therein. (b) Horiuchi, C. A.; Ikeda, A.; Kanamori, M.; Hosokawa, H.; Sugiyama, T.; Takahashi, T. T. *J. Chem. Res., Synop.* **1997**, 60−61.

ring opening of styrene oxide was shown not to be highly regioselective (entry 5). In addition, the optical purity of the styrene oxide regenerated from iodohydrin **28** (NaOMe/MeOH) was found to have eroded from 98 to only 35%, suggesting significant involvement of the S_N1 pathway for the formation of **28** from styrene oxide.

As part of our continuing interest in developing new methods for the glycosylation of alcohols, phenols, and other pharmacologically important molecules, it was discovered that the Ferrier-type glycosylation can take place in a highly efficient manner in the presence of catalytic iodine.[6] While the exact mechanism of this unique reaction remains to be elucidated, preliminary evidence suggests that the glycosylation proceeds as a result of the production of small amounts of HI from the iodine and substrate. Therefore, it was felt that anhydrous HI produced by the oxidation of a thiol with iodine might also be an effective catalyst for the Ferrier-glycosylation reaction.[19] In this regard, the glycoside donor tri-*O*-acetyl glucal was treated with various acceptors in the presence of catalytic amounts of HI (Table 4). It was found that glycosylated products **32** and **33** were obtained stereoselectively in quantitative yield in less than 30 min with 5 mol % of the catalyst with simple glycosyl acceptors (entries 1 and 2). A 1,6-linked disaccharide, **37**, was obtained in excellent yield (80%, purified) by this method with good anomeric stereoselectivity (entry 5). Glycosylation of thiol acceptors, while practical in a few cases (see entries 3 and 4), are less efficient in certain cases due to the competing reaction of the thiol with iodine.

In summary, we have shown that anhydrous HI (1 mol equiv) in dichloromethane can be generated quantitatively from the oxidation of a thiol compound (1 mol equiv) by solid iodine (0.5 mol equiv) in the presence of a substrate that reacts with the in situ generated HI. The HI thus generated has been employed for the highly stereocontrolled synthesis of α-glycosyl iodides and vicinal iodohydrins from their corresponding per-*O*-acetyl carbohydrates and epoxides, respectively (both with stoichiometric HI) and for catalysis of the Ferrier glycosylation of alcohols and thiols (with catalytic HI). The byproduct disulfides **5** and **7** (see Table 1) have shown no adverse effect on the outcome of these reactions. Further applications on the use of this conveniently generated anhydrous HI in synthesis are currently under investigation.

Table 4. HI-Catalyzed Glycosylation of Alcohols and Thiols

entry	acceptor	method[a]	product	% yield[b]	α/β[c]
1	*i*-PrOH	A	 **32**	~100	4.6 : 1
2	$PhCH_2OH$	B	 **33**	~100	3.3 : 1
3	*n*-PrSH	A	 **34**	41	7.0 : 1
4	PhSH	A	 **35**	69	4.0 : 1
5	 **36**	B	 **37**	80	6.3 : 1

[a] Method A: 5 mol % of HI generated from I_2 and thiolacetic acid (**4**) in CH_2Cl_2. Method B: 5 mol % of HI generated from I_2 and 1,3-propanedithiol (**6**) in CH_2Cl_2. [b] Yield of isolated, chromatographically pure products. [c] Ratio of the two anomers at the newly created glycosylic centers.

Supporting Information Available: Experimental procedures and characterization data for the new compounds described. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Bajwa, J. S.; Anderson, R. C. *Tetrahedron Lett.* **1991**, *32*, 3021−3024.
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