Mild and Efficient Hydrolysis of Thioglycosides to Glycosyl Hemiacetals Using *N*-Iodosaccharin[1]

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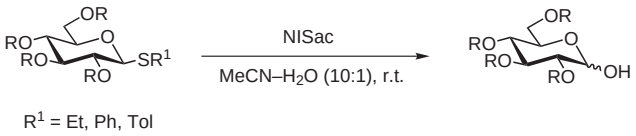
Abstract: A convenient methodology has been developed for the mild hydrolysis of thioglycosides to the corresponding hemiacetals using *N*-iodosaccharin without any requirement of co-activator. Most of the functional groups used for the protecting group manipulation of carbohydrates remain unaffected under the reaction conditions.

Key words: carbohydrate, hydrolysis, thioglycoside, hemiacetals, *N*-iodosaccharin

Suitably functionalized glycosyl hemiacetals are useful intermediates for the preparation of various glycosyl donors used in the synthesis of oligosaccharides.[2–4] They can be converted into more reactive glycosyl donors such as glycosyl fluorides,[5] trichloroacetimidates[6] and as such can be used in dehydrative glycosylation reactions.[7] They have also been applied in Wittig or Horner–Emmons or related reactions for chiral synthesis of various natural products.[8,9] Glycosyl hemiacetals can be prepared from (a) peracetylated sugars using hazardous hydrazine salts[10] or organic bases like benzyl amine[11] or under acidic conditions;[12] (b) acid hydrolysis of alkyl glycosides;[13] or (c) hydrolysis of thioglycosides. Among them, hydrolysis of thioglycosides is more useful as it provides the preparation of glycosyl hemiacetals having diverse functionalities under mild reaction conditions. As expected, a number of reports appeared in the literature for this purpose, including the use of toxic heavy metal salts,[14] *N*-bromosuccinimide (NBS)[15] or *N*-iodosuccinimide (NIS) alone[16] or in the presence of an acid,[17–19] borate salts/*n*-$Bu_4NIO_4/HClO_4$,[20] $V_2O_5/H_2O_2/NH_4Br$,[21] $(NH_4)_6Mo_7O_{24}/H_2O_2HClO_4/NH_4Br$,[22] and chloramine-T.[23] However, many of these methods suffer from limitations, such as use of expensive reagents, incompatibility with acidic functional groups, relatively low yield and sometime harsh reaction conditions. In search of a generalized reaction condition for the hydrolysis of thioglycosides having acid-labile and base-labile functional groups, we have tested the efficacy of *N*-iodosaccharin (NISac) for this purpose. Recently, NISac has been used in the glycosylation reaction using armed glycosyl donors[24] and iodination of alkenes[25] and conversion of alcohols to iodides.[26] As discussed earlier,[24] due to the lower pK_a value of NISac (pK_a 1.30) than its analogous NIS (pK_a 9.62), it should be a more potent iodinating agent than NIS and it should activate thioglycosides without the requirement of any strong acid as co-activator. Taking cues from the literature reports, we have reasoned that NISac could independently activate thioglycosides in a moist reaction condition resulting in the formation of hemiacetals. Avoiding the addition of acidic co-activator could make this method equally effective for hydrolyzing thioglycosides having both acid-labile as well as base-labile protecting groups. *N*-Iodosaccharin can be easily prepared[25] in the laboratory and it is very much cost-effective in comparison to analogous *N*-iodosuccinimide (NIS).



Scheme 1

In an initial set of experiments, ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside was treated with 1.5 equivalents of NISac in wet acetonitrile (MeCN–H_2O = 10:1) at room temperature (Scheme 1). To our satisfaction, a clean formation of glycosyl hemiacetal was achieved in almost quantitative yield in only five minutes. Reducing the quantity of NISac resulted in incomplete hydrolysis of thioglycoside even after 24 hours. Similar reaction conditions were then applied to hydrolyze a diverse set of thioglycosides containing base-labile and acid-labile functional groups, which is presented in Table 1. In Table 1, there are a number of points that need to be highlighted. All reactions were complete in 5–30 minutes. The reaction condition is compatible with the acid-labile functional groups (benzylidene, isopropylidene, silyl ether, 4-methoxybenzylidene) as well as base-labile groups (acetyl, benzoyl, chloroacetyl). Interglycosidic linkage remains unaffected under the reaction condition. The rate of activation depends on the alkyl or aryl part linked to the sulfur atom; thus the SPh group takes a longer time to hydrolyze than the SEt or STol glycosides. The rate of hydrolysis for the acyl-protected thioglycosides is slightly slower than the alkyl-protected counterpart, which may be explained by considering the 'armed-disarmed' concept. In most of the cases, an anomeric mixture of glycosyl hemiacetals was formed and the ratio was determined from the ^1H NMR of the crude products. A series of solvents has been tested for the reaction

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and MeCN–H_2O (10:1) mixture has been found to be the best option in comparison to other commonly used solvents like dichloromethane and THF. In contrast to the earlier report,[24] no trace of formation of glycosyl saccharine derivatives was observed. The formation of the product could be explained by considering the formation of sulfonium ion generated by NISac activation of thioglycoside followed by hydrolysis.

In summary, a relative shortcoming of the hydrolysis of thioglycosides has been overcome by devising a generalized, mild reaction protocol for the hydrolysis of thioglycosides without requirement of any co-activator. Most of the functional groups used for the protecting group manipulation of carbohydrate were found unaffected under the reaction condition. It is important to mention that *N*-iodosaccharine (NISac) is very cheap in comparison to its closest analogue, *N*-iodosuccinimide (NIS). Straightforward operation, low-cost activator, very short reaction time, and simple purification of products are the key features of this generalized protocol, which makes it an attractive alternative to the existing literature procedures.

Table 1 Hydrolysis of Thioglycosides Using *N*-Iodosaccharin (NISac) at Room Temperature[27]

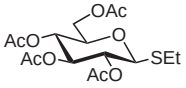
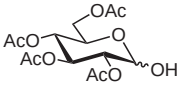
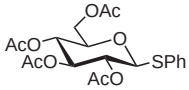
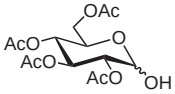
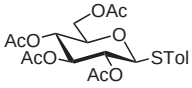
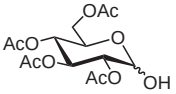
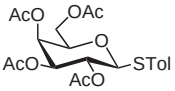
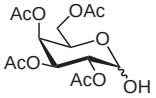
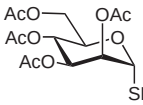
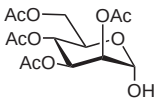
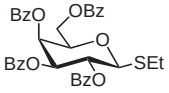
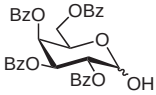
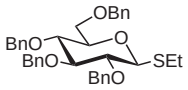
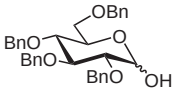
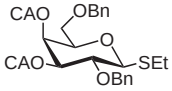
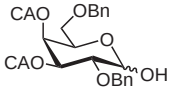
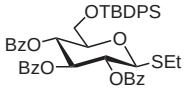
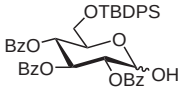
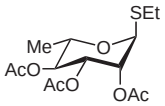
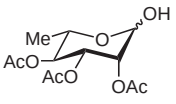
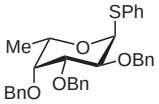
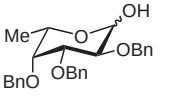
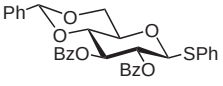
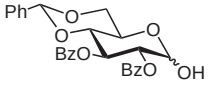
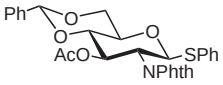
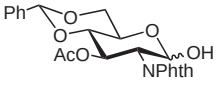
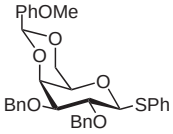
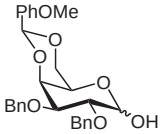
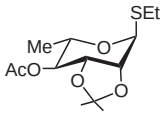
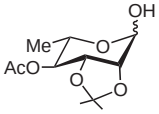
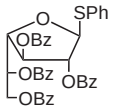
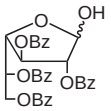
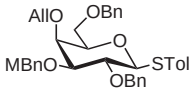
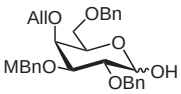
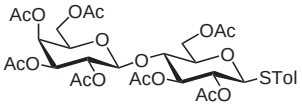
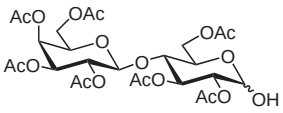
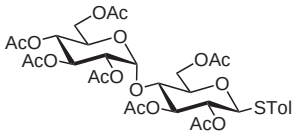
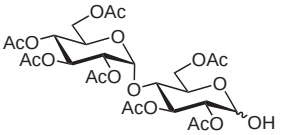
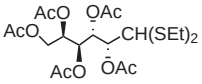
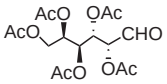
Entry	Thioglycosides **1**[a]	Products **2**[a]	Time (min)	Yield (%)	α/β	Ref.
1			5	95	3:1	21
2			20	92	3.5:1	21
3			5	95	3:1	21
4			5	92	2.5:1	21
5			20	90	1:0	21
6			5	92	3:1	21
7			3	88	2:1	23
8			3	85	3:1	21
9			5	95	2.5:1	21
10			5	92	4:1	12
11			3	90	5:1	21
12			30	90	1:1	21

Table 1 Hydrolysis of Thioglycosides Using *N*-Iodosaccharin (NISac) at Room Temperature[27] (continued)

Entry	Thioglycosides **1**[a]	Products **2**[a]	Time (min)	Yield (%)	α/β	Ref.
13			20	90	1:2	–
14			20	85	2:1	23
15			5	92	3:1	23
16			10	82	5:1	21
17			5	80	2:1	21
18			5	95	2:1	21
19			5	95	2:1	21
20			20	80[b]	–	–

[a] Tol = tolyl; CA = chloroacetyl; Phth = phthalimido; MBn = 4-Methoxybenzyl.
[b] NISac (2.5 equiv) was used.

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(27) **Typical Experimental Procedure**: To a solution of thioglycoside (1.0 mmol) in MeCN–H_2O (10:1; 5 mL) was added *N*-iodosaccharin (1.5 mmol) at r.t. and the reaction mixture was allowed to stir for the time mentioned in Table 1. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The crude mass was purified over SiO_2 using hexane–EtOAc as eluent to furnish the pure glycosyl hemiacetal as an anomeric mixture. Products of all known compounds gave acceptable ^{1}H NMR and ^{13}C NMR spectra that matched the data reported in the cited references.[28]
(28) Spectral data of selected compounds:
3-*O*-Acetyl-4,6-*O*-benzylidene-2-deoxy-2-phthalimido-D-glucopyranose (Table 1, Entry 13): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.91 (m, 9 H, aromatic protons), 5.85 (t, *J* = 9.0 Hz, 1 H, H-3), 5.69 (d, *J* = 8.1 Hz, 1 H, H-1), 5.58 (s, 1 H, PhC*H*), 4.48 (dd, *J* = 4.5, 10.2 Hz, 1 H, H-4), 4.35–4.40 (m, 1 H, H-2), 3.70–3.83 (m, 3 H, H-5, H-6a, H-6b), 1.88 (s, 3 H, OCOMe). ESI-MS: *m*/*z* calcd for $C_{23}H_{21}NO_8$: 439; found: 462 $[M + Na]^+$.
2,3,4,5,6-Penta-*O*-acetyl-D-galactose (Table 1, Entry 20): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.04–2.12 (5 × s, 15 H), 3.91 (dd, 1 H), 4.26 (dd, 1 H), 5.26 (d, *J* = 2.0 Hz, 1 H), 5.36 (m, 1 H), 5.49 (d, *J* = 8.0 Hz, 1 H), 5.62 (d, *J* = 8.0 Hz, 1 H), 9.45 (br s, 1 H). ESI-MS: *m*/*z* calcd for $C_{16}H_{22}O_{11}$: 390; found: 413 $[M + Na]^+$.