Mild and efficient hydrolysis of thioglycosides to glycosyl hemiacetals using N-iodosaccharin 1

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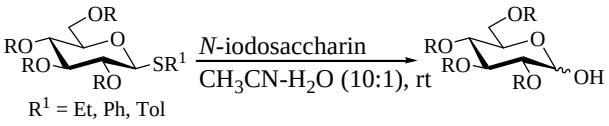
Abstract: A convenient methodology has been developed for the mild hydrolysis of thioglycosides to the corresponding hemiacetals using N-iodosaccharin without any requirement of co-activator. Most of the functional groups used for the protecting group manipulation of carbohydrates are remain unaffected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

Key words: Carbohydrate, hydrolysis, thioglycoside, N-iodosaccharin, hemiacetals.

Suitably functionalised glycosyl hemiacetals are useful intermediates for the preparation of various glycosyl donors used in the synthesis of oligosaccharides.2-4 They can be converted to more reactive glycosyl donors such as glycosyl fluorides,5 trichloroacetimidates6 and as such can be used in the dehydrative glycosylation reactions.7 They have also been successfully 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 salts10 or organic bases like benzyl amine11 or under acidic conditions reported from our laboratory;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. Therefore, hydrolysis of thioglycosides is quite often used for the preparation of glycosyl hemiacetals. As expected, a number of reports appeared in the literature for this purpose, which include, the use of toxic heavy metal salts,14 N-bromosuccinimide (NBS)15 or N-iodosuccinimide (NIS)16 in wet acetone, NBS/HCl,17 boratesalts/nBu4NIO4/HClO4,18 (NH4)6Mo7O24-H2O2-HClO4 -NH4Br,19 V2O5-H2O2-NH4Br,20 chloramine-T,21 NIS-TfOH,22 NIS-TFA23 etc. However, many of these methods suffer from limitations such as, use of expensive reagents, incompatibility with acidic functional groups present in the substrates, relatively low yield and sometime harsh reaction conditions. Therefore, the development of a mild, efficient and metal-free reaction condition is always welcome. 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 donors24 and iodination of alkenes25 and conversion of alcohols to iodides.26 As discussed earlier,24 due to the low pKa value of NISac (pKa = 1.30) than it's analogous NIS (pKa = 9.62), it should be 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 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 prepared25 in the laboratory and it is very much cost-effective in comparison to analogous N-iodosuccnimide (NIS).



Scheme 1

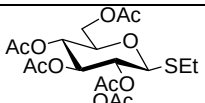
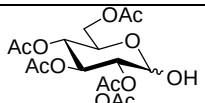
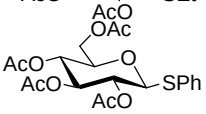
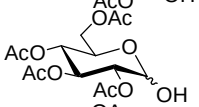
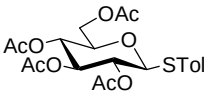
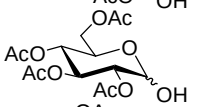
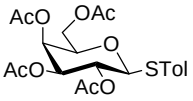
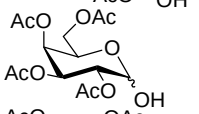
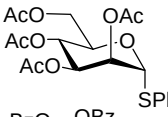
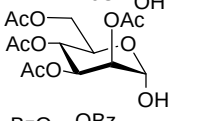
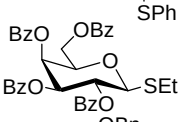
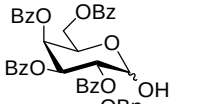
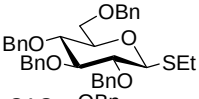
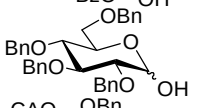
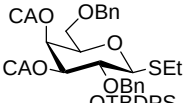
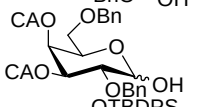
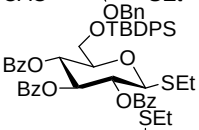
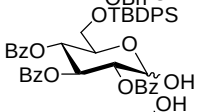
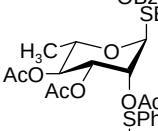
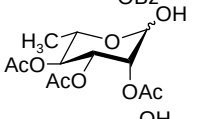
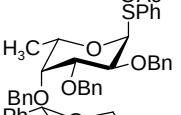
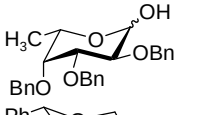
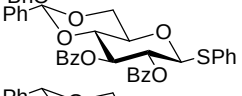
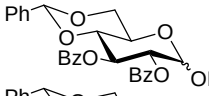
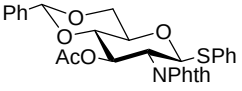
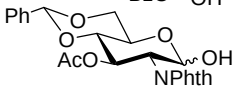
In an initial set of experiments, ethyl 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranoside was treated with 1.5 equiv NISac in wet acetonitrile (CH3CN:H2O = 10:1) at room temperature (Scheme 1). To our satisfaction, a clean formation of glycosyl hemiacetal was achieved in almost quantitative yield in only 5 min. Reducing the quantity of NISac resulted an incomplete hydrolysis of thioglycoside even after 24 h. Similar reaction condition was 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 completed in 5-30 min. The reaction condition is compatible to 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, such as, SPh group takes longer time to get hydrolyzed than SEt ot Stolyl glycosides. The rate of hydrolysis of acyl-protected thioglycosides is slightly slower than alkyl-protected counterpart, which may be explained by considering "armed-disarmed" concept. In most of the cases, an anomeric mixture of glycosyl hemiacetals were formed and the ratio was determined from the 1H NMR of the crude products. A series of solvents have been tested for the reaction and CH3CN-H2O (10:1) have been found best suitable in comparison to other commonly used solvents like dichloromethane and THF. In contrast to the earlier report,24 no trace of formation of

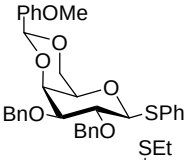
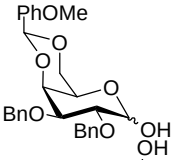
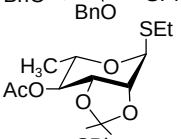
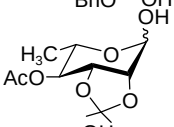
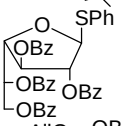
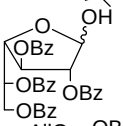
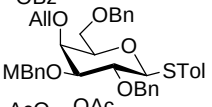
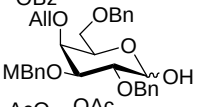
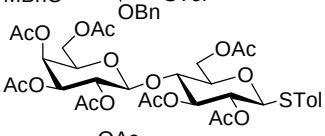
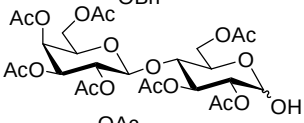
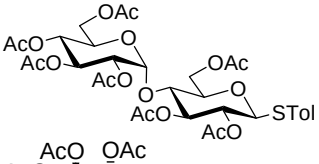
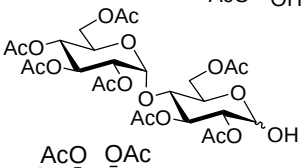
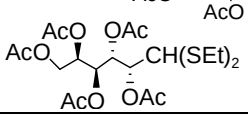
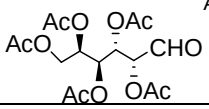
glycosyl saccharine derivatives were observed. The formation of the product could be explained by considering the formation of sulfonium ion generated by NISac activation of thioglycoside followed by hydrolysis.

A typical experimental procedure: To a solution of thioglycoside (1.0 mmol) in CH3CN-H2O (10:1; 5 mL) was added N-iodosaccharin (1.5 mmol) at room temperature and the reaction mixture was allowed to stir for appropriate time as mentioned in Table 1. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The crude mass was purified over SiO2 using hexane-EtOAc as eluent to furnish pure glycosyl hemiacetal as an anomeric mixture. Products of all known compounds gave acceptable 1H NMR and 13C NMR spectra that matched the data reported in the cited references.27

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 analog, 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 for which it may be considered as an attractive alternative to the existing literature procedures.

Table 1. Hydrolysis of thioglycosides using N-iodosaccharin (NISac) at room temperature.

Entry	Thioglycosides (1)	Products (2)	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
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	80a	-	-

Stol: S-tolyl; CA: chloroacetyl; NPhth: N-phthalimido. a 2.5 equiv. of NISac was used

Acknowledgment

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25. Spectral data of selected compounds:
26. 3-O-acetyl-4,6-O-benzylidene-2-deoxy-2-phthalimido-D-glucppyranose (Entry 13, Table 1): 1H NMR (CDCl3, 300 MHz): δ 7.91-7.33 (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, PhCH), 4.48 (dd, J = 10.2 Hz, 4.5 Hz, 1 H, H-4), 4.40-4.35 (m, 1 H, H-2), 3.83-3.70 (m, 3 H, H-5 and H-6a,b), 1.88 (s, 3 H, OCOCH3); m/z for C23H21NO8: 439 (calcd), 462 [M+Na] (found).
27. 2,3,4,5,6-Penta-O-acetyl-D-galactose (Entry 20, Table 1): 1H NMR (CDCl3, 300 MHz): δ 2.04-2.12 (5s, 15H), 3.91 (dd, 1H), 4.26 (dd, 1H), 5.26 (d, J = 2.0 Hz, 1H), 5.36 (m, 1H), 5.49 (d, J = 8.0 Hz, 1H), 5.62 (d, J = 8.0 Hz, 1H), 9.45 (bs, 1H); m/z for C16H22O11: 390 (calcd), 413 [M+Na] (found).