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Glycosylation reactions with 'disarmed' thioglycoside donors promoted by *N*-iodosuccinimide and $HClO_4$–silica

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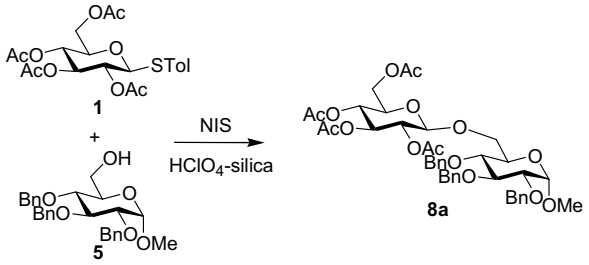
Abstract—Glycosylation of 'disarmed' thioglycosides promoted by NIS in the presence of $HClO_4$ immobilized on silica compares very favourably with the accepted NIS–TfOH procedure.

Understanding the role of glycosylation in biology is highly dependent on the development of new chemical glycosylation techniques to provide rapid, straightforward access to synthetic glycoconjugates.[1] In the last few years, remarkable improvements have been made through orthogonal glycosylation strategies, reactivity tuning methodologies based on 'armed' and 'disarmed' glycosylation reagents[2,3] and instrument-based automated glycosylation strategies.[4] Of the building blocks in common use, the stability and ease of handling of thioglycosides makes them particularly attractive glycosyl donor agents.[5] In the search for simpler, practical chemistries for preparing oligosaccharides, we have developed procedures for the efficient synthesis[6] and activation of thioglycosides.[7] A key contribution to glycosylation with thioglycosides was made in 1990 by van Boom and co-workers,[8] who first reported the use of *N*-iodosuccinimide (NIS) in conjunction with triflic acid as a promoter to activate 'disarmed' thioglycosides. The same reagent combination was also introduced in 1990 by Fraser-Reid and co-workers for the activation of 'disarmed' pentenyl glycosides;[9] more recently, this work was extended to explore ytterbium triflate in conjunction with NIS for the activation of *n*-pentenyl orthoesters.[10] The use of salts of strong acids in conjunction with *N*-bromosuccinimide to activate thioglycosides has been investigated by Kusumoto and co-workers.[11] Recent reports of the use of perchloric acid immobilized on silica ($HClO_4$–silica) as an effective acid catalyst for sugar acetylation[12] and Ferrier rearrangement of glycals[13] drew us to investigate the application of this reagent in combination with NIS for thioglycoside activation.[14] Herein, we describe the use of $HClO_4$–silica as a practical alternative to triflic acid for NIS-promoted glycosylation reactions with 'disarmed' thioglycosides.

Initial investigations,[15–17] employing 1.1 mol equiv NIS and ca. 80 mg of $HClO_4$–silica per mmol of donor, focused on the reaction of *p*-tolyl 2,3,4,6-tetra-*O*-acetyl-β-D-thioglucopyranoside **1** with the primary alcohol of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **5** in dichloromethane at 0 °C. Reaction was essentially complete within 1 h, affording the expected 1,2-*trans*-disaccharide **8a** in 82% yield after chromatographic purification (Scheme 1). Control experiments with silica replacing $HClO_4$–silica showed no significant reaction



Scheme 1. Thioglycoside glycosylation promoted by NIS/$HClO_4$–silica.

Keywords: Glycosylation; Thioglycoside; NIS; Perchloric acid–silica.
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Table 1. Results of NIS/$HClO_4$ promoted glycosylation reactions with 'disarmed' thiglycoside donors

Acceptors / Donors	**5**	**6**	**7**
1	**8a** (82%)	**8b** (81%)	**8c** (83%)
2	**9a** (85%)	**9b** (79%)	**9c** (81%)
3	**10a** (74%)	**10b** (78%)	**10c** (76%)
4	**11a** (87%)	**11b** (80%)	**11c** (85%)

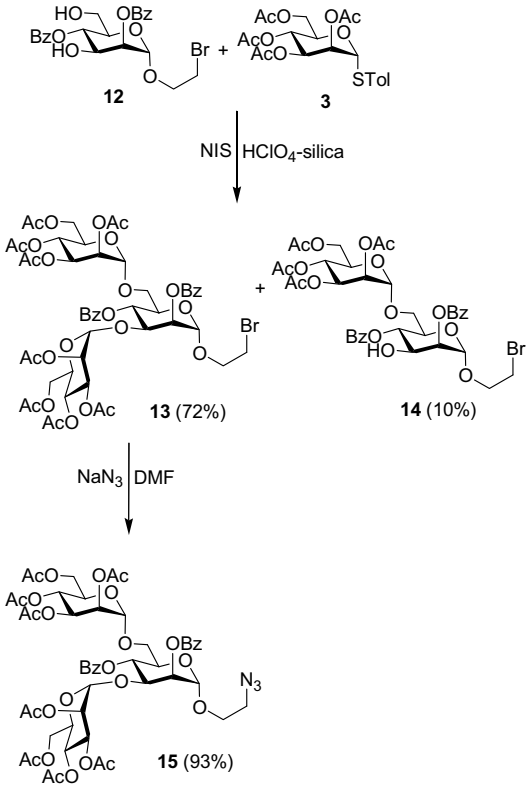
Yields in parentheses are those after chromatographic purification.

over 5 h, illustrating that silica is not itself sufficiently acidic to activate NIS.

Looking more broadly, a series of NIS/$HClO_4$–silica promoted reactions were investigated with representative 'disarmed' thioglycoside donors **1**–**4** and a systematic series of glycosyl acceptors, **5**–**7**. In all cases, reactions gave excellent results, providing the expected 1,2-*trans*-linked disaccharides in 74–87% isolated yields (Table 1).[17] Reactions were typically complete in no more than 1 h at ice-bath temperature, with reactions employing the more reactive deoxyhexose (rhamnose) donor **4** complete in ca. 1/2 h. In the case of the C-2 axial mannoside donor **3**, isolated yields of the disaccharides were somewhat lower due to formation of the hemiacetal by hydrolysis of the orthoester intermediate formed during the glycosylation reaction. Presumably the greater inherent reactivity of the corresponding rhamnoside overcomes this issue.

Extending to a one-pot double glycosylation, synthesis of the *N*-linked glycan trimannoside core [3,6-di-*O*-(α-D-mannopyranosyl)-α-D-mannopyranoside] in a form suitable for conjugation to surfaces was investigated. Reaction of acceptor **12** with 2.6 equiv of donor **3** afforded trisaccharide **13** in 72% yield, along with 10% of the 1,6-linked disaccharide **14** (Scheme 2). Conversion of the alkyl halide **13** to known azide **15**[18] was then effected with NaN_3 in DMF in good yield.

In conclusion, $HClO_4$–silica in combination with *N*-iodosuccinimide is a very effective promoter for 1,2-*trans*-glycosylation reactions with 'disarmed' thioglycoside donors. $HClO_4$–silica is much easier to handle and store than the triflic acid typically used for glycosylation reactions of this nature.



Scheme 2. Synthesis of a known[18] protected derivative of the *N*-linked glycan trimannoside core.

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15. $HClO_4$–silica was prepared essentially as described previously,[13a] except that it was dried for 2 h at 110 ° C instead of for 6 h.
16. Typical glycosylation procedure: a mixture of **1** (1.3 mmol), **6** (1 mmol) and 4 Å MS in dry CH_2Cl_2 (20 mL) was cooled to 0 °C. NIS (1.5 mmol) was added followed by $HClO_4$–silica (100 mg) and stirring was continued until complete consumption of **6** (TLC). The mixture was filtered through Celite® and the filtrate was washed with aq Na_2SO_3 solution, aq $NaHCO_3$ solution and H_2O. After drying and evaporation of the organic layer, the crude product was purified by flash chromatography using *n*-hexane–EtOAc (2:1).
17. Known compounds gave analytical data consistent with the literature: **5**,[19] **6**,[20] **7**,[21] **8a**,[22] **b**[23] and **c**[9] and **9a**,**b**.[24] All new compounds gave analytical data (^1H, ^{13}C NMR and HRMS) consistent with the structures given.
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