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Tri-isopropylsilyl thioglycosides as masked glycosyl thiol nucleophiles for the synthesis of *S*-linked glycosides and glyco-conjugates

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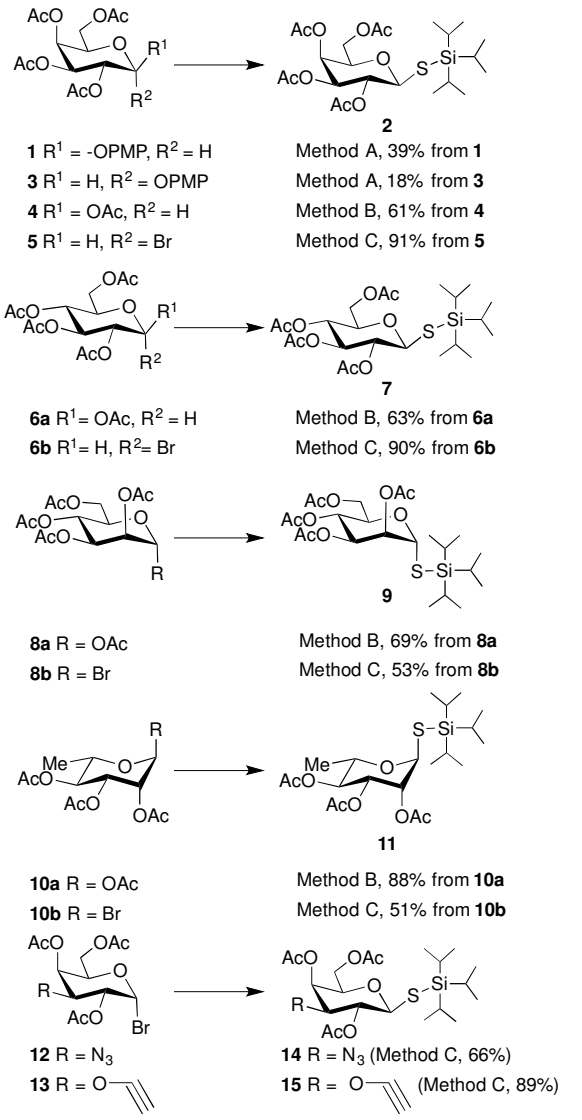
Abstract: Tri-isopropylsilyl thio-glycosides (TIPS S-glycosides) were synthesized through base promoted S_N2 substitution of glycosyl halides with TIPS-SH or by Lewis acid promoted glycosylation of TIPS-SH with glycosyl acetates or *p*-methoxyphenyl glycosides. Various thioglycoside derivatives were obtained in high yields by one-pot fluoride-mediated de-silylation and thiol alkylation with alkyl halides or Michael acceptors of one common TIPS S-glycoside.

Development of the glycomimetics is an important area of research due to their potential as biological tools and in pharmaceutical applications.[1, 2] A large and important class of glycomimetics include stable analogues in which one or more oxygen atoms, *i.e.* glycosidic oxygens, have been replaced by *e.g.* sulfur[3, 4] or other heteroatoms,[5] leading to structures more tolerable towards enzymatic and acidic hydrolysis and thus with enhanced stability in biological environments. Hence, the enhanced hydrolytic stability of thioglycosides,[3, 4] makes them particularly useful as tools in investigations of glycoconjugate functions. Examples include thioglycosides as key mediators for cellular surface recognition and enzyme inhibitors,[6] and thioglycosides binding to many lectins,[7] *e.g.* the unnatural disaccharide thiodigalactoside binding to galectins with about the same affinity as LacNAc.[8] Indeed, thiodigalactoside shows promising immune-promoting properties against tumor cells[9] and its derivatives have been shown to attenuate tumor motility,[10] macrophage differentiation,[11] fibrosis progression,[12] hepatitis,[13] and pancreatic islet cell apoptosis.[14]

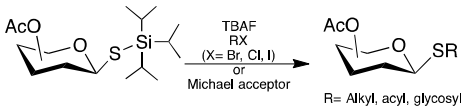
Furthermore, thioglycosides are being used as versatile donors and thus key precursors in oligosaccharide synthesis, synthesis of glycodendrimers,[15, 16] sulfur containing glycolipids,[4] and S-linked protein glycoconjugates.[17, 18] In such use of thioglycosides, the chemical properties of the thioglycoside aglycon part typically influences reactivity and reaction outcome, why methods for easy diversification of the thio-glycoside aglycon is of interest. Thioglycoside synthesis is usually performed by S_N2 displacement of a glycosyl halide by a thiol(ate) or by Lewis acid-catalysed glycosylation of a thiol with glycosyl acetates or phenyl *O*-glycosides.[4, 5] Additional methods include *in situ* aminolysis and alkylation of thioacetates,[19, 20] Michael type addition of 1-thiolates to carbohydrate enones,[21] coupling of glycals and thiols in Ferrier-type reactions,[22] thiol-ene click reactions,[21] ring opening of carbohydrate epoxides with thiols,[23] the use of Lawesson's reagent with hemiacetals,[24] formation of □-thio-glycosidic linkage from 1,6-anhydro derivatives with bis-(trimethylsilyl) sulfide,[25] formation of β-thioglycosidic linkages by the use of Na_2S and CS_2,[4] and Michael type reactions involving a thirane intermediate.[4] In case a collection of thio-glycosides carrying diverse aglycon structures is needed, a majority of these methods would require that a separate (glycosylation) reaction with a thiol was undertaken for each member of the collection. Triisopropylsilyl sulfides are remarkably stable,[26] yet mildly de-silylated and alkylated in the presence of fluoride sources.[27-29] Triisopropylsilyl thio-glycosides are known and their de-silylation have been demonstrated,[30] but have not been evaluated as masked glycosyl thiolate nucleophiles for *in situ* activation and reaction with electrophiles. Herein, we report on a novel, rapid, and effective synthetic method towards different thio-glycosides in one step within 5 min by reacting electrophiles with readily accessible tri-isopropylsilyl thio-glycosides as common precursors in the presence of tetrabutylammonium fluoride.

Boron trifluoride etherate-catalysed glycosylation of tri-isopropylsilylthiol (TIPSSH) with anomeric acetates or *p*-methoxy phenyl glycosides, as well as S_N2 displacement of anomeric bromides by TIPSSH in presence of a base K_2CO_3, resulted in stereoselective formation of TIPS thio-glycosides (Scheme 1). Evaluation of reaction conditions for the Lewis acid-



Scheme 1. Synthesis of tri-isopropylsilyl thio-glycosides: [a]Method A: $BF_3.Et_2O$, TIPSSH, Dry Toluene. Method B: $BF_3.Et_2O$, TIPSSH, Dry DCM. Method C: K_2CO_3, TIPSSH, Dry Acetone.

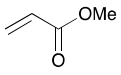
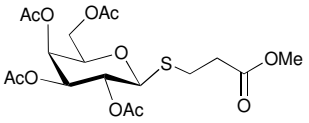
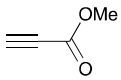
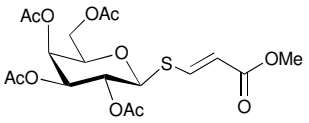
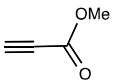
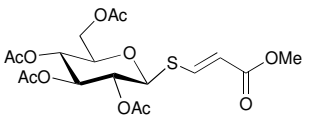
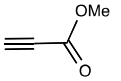
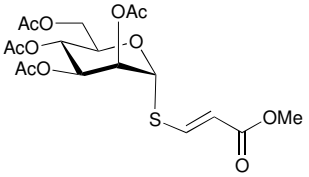
mediated activation of glycosyl acetates and *p*-methoxyphenyl β-glycosides revealed that dichloromethane was a solvent superior to toluene, diethyl ether, and acetonitrile for activation of glycosyl acetates (**4**, **6a**, **8a**, **10a**), while toluene[31] was the best solvent with *p*-methoxyphenyl β-galactoside as donors (1). Furthermore, boron trifluoride etherate proved to be the best choice of Lewis acid over TMSOTf. Among different conditions investigated for the displacement of glycosyl bromides (**5**, **6b**, **8b**, **10b**, **12**, **13**) under basic conditions, NaH in DMF, Cs_2CO_3 in DMF, and K_2CO_3 in acetone, the best result were obtained with K_2CO_3 in acetone. While reasonable yields were obtained by boron trifluoride etherate activation of glycosyl acetates (**4**, **6a**, **8a**, **10a**) and *p*-methoxyphenyl β-galactoside **1**, the best yields for formation of TIPS thio-glycosides were obtained by using glycosyl bromides (**5**, **6b**, **12**[32], **13**[33]) in the presence of base. For mannose and rhamnose the best yields were achieved with Lewis acid-promoted activation of anomeric acetates (**8a** and **10a**).



Scheme 2. General scheme for cleavage and *in situ* alkylation of STIPS glycosides.

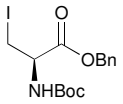
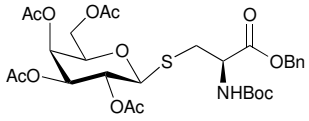
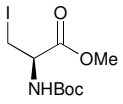
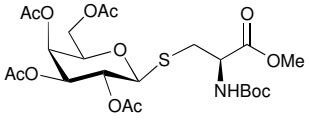
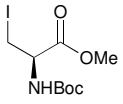
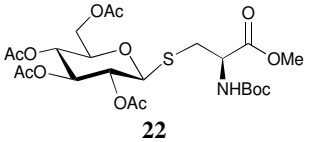
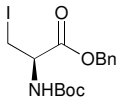
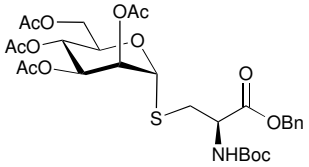
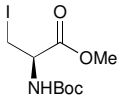
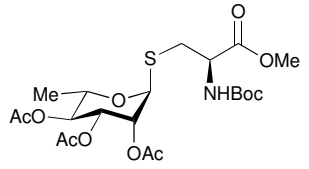
Cleavage and *in situ* alkylation of STIPS sulfides have been demonstrated to be efficient with fluoride sources.[27] Hence, the S-Si bond of the TIPS thioglycosides (**2**, **7**, **9**, and **11**) was found to be easily transformed into various thioglycosides by activation with fluoride ions in presence of an electrophile (Michael acceptor, alkyl halide, acid chloride, or glycosyl bromide) in a high-yielding and stereoselective reaction at RT in 5 min on both small and large (gram) scale (Scheme 2). Michael acceptors are known to be highly efficient electrophiles in reaction with thiol(ate) nucleophiles, which proved to also be the case with the conditions for de-silylating and activating TIPS thioglycosides with TBAF (Table 1). Michael additions to methyl propiolate afforded the more stable *E*-isomer exclusively (compounds **17**, **18**, and **19**; Table 1) according to NMR analysis. Hence, the method is of potential value for the construction of hydrolytically stable glycomimetics via thiolate Michael additions.

Table 1 One-pot de-silylation and glycosyl thiol alkylation with Michael acceptors[a]

Cpd	Electrophile	Thioglycoside product	Yield (%)
2		 **16**	91
2		 **17**	93
7		 **18**	95
9		 **19**	94

[a]STIPS glycoside (1 eq.), Michael acceptor (1.3 eq.), MeCN (26 mL/mmol STIPS glycoside), TBAF (1.2 eq., 1.0 M in THF), 5 min.

Table 2 One-pot de-silylation and glycosyl thiol alkylation with β-iodo-L-alanine esters[a]

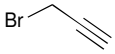
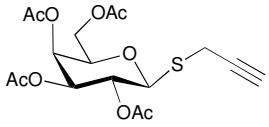
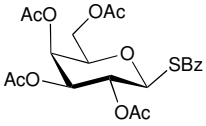
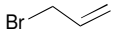
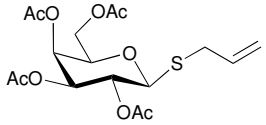
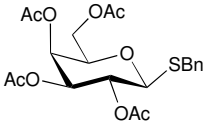
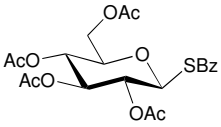
Cpd	Electrophile	Thioglycoside product	Yield (%)
2		 **20**	91
2		 **21**	93
7		 **22**	94
9		 **23**	93
11		 **24**	94

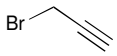
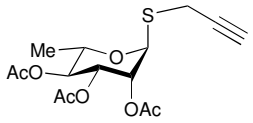
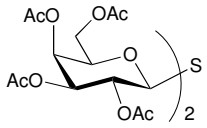
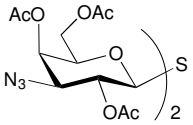
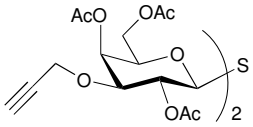
[a]STIPS glycoside (1 eq.), b-iodo-L-alanine ester (1.2 eq.), MeCN (26 mL/mmol STIPS glycoside), TBAF (1.2 eq., 1.0 M in THF), 5 min.

Neoglycopeptides and proteins are important as research tool is glycobiology and S-glycosylated cysteine derivatives are useful building blocks for such structures. Reaction of *N*-Boc-protected β-iodo-L-alanine ester derivatives with TIPS thio-glycosides in presence of TBAF in acetonitrile at RT for 5 min furnished the corresponding L-cysteine derivatives **20**-**24** in excellent yields (Table 2). Hence, the method provides an efficient one step protocol with minimal formation of *e.g.* eliminated by-products.

To further explore of the method, TIPS thio-β-glycosides were evaluated as masked sulfur nucleophiles with alkyl, acid, and glycosyl halides, including substituted galactosyl bromides (**12**[32] and **13**[33]), under the same reaction conditions as described above (Table 3). All reactions proceeded smoothly to furnish the corresponding alkyl β-thioglycosides **25**, **27**-**28**, and **30**, glycosyl thio-benzoates **26** and **29**, and thiodigalactosides **31**-**33** in excellent yields. In particular, the examples involving synthesis of thiodigalactoside derivatives **31**-**33** are illustrative of the high efficiency of the STIPS glycosides in the synthesis of thioglycosides as other methods for synthesis of thiodiglycosides including those using glycosyl thiouronium intermediates as masked glycosyl thiolate nucleophiles provide significantly less clean reactions and substantially lower yields in our hands and in published work by others.[34-36] Furthermore, formation of glycosyl thiouronium intermediates commonly require reaction at higher temperature with thiourea and in many cases the glycosyl thiouronium intermediates show limited stability upon storage.

Table 3 One-pot de-silylation and glycosyl thiol alkylation with alkyl, acyl, and glycosyl halides[a]

Cpd	Electrophile	Thioglycoside product	Yield (%)
2		 **25**	97
2	BzCl	 **26**	96
2		 **27**	98
2	BnBr	 **28**	98
7	BzCl	 **29**	97

11		 **30**	98
2	**5**	 **31**	88
14	**12**[32]	 **32**	95
15	**13**[33]	 **33**	93

[a]STIPS glycoside (1 eq.), alkyl (1.3 eq), acyl (1.3 eq), or glycosyl halide (1 eq.), MeCN (26 mL/mmol STIPS glycoside), TBAF (1.2 eq., 1.0 M in THF), 5 min.

Conclusions

In summary, this report presents an efficient and convenient one-pot protocol for stereoselective synthesis of thioglycoside derivatives by room temperature and one-pot TBAF-mediated de-silylation and nucleophilic reactions of storage-stable TIPS thio-glycosides towards Michael acceptors, as well as alkyl, acyl, and glycosyl halides in high yields.

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Notes and references

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Electronic Supplementary Information (ESI) available: Experimental procedures, Characterization data and copies of ^{1}H and ^{13}C NMR of all compounds and COSY and HMQC for selected compounds. See DOI: 10.1039/c000000x/

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