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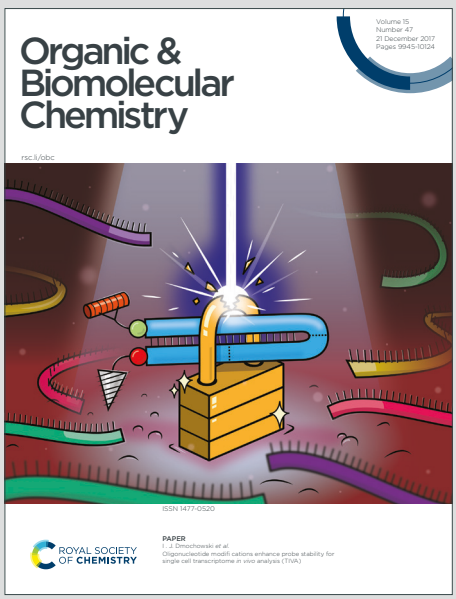

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Sub-Stoichiometric Reductive Etherification of Carbohydrate Substrates and One-Pot Protecting Group Manipulation

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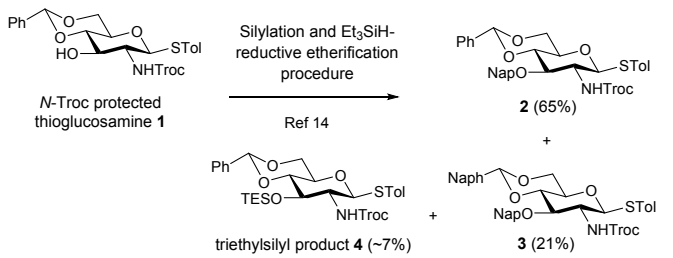
In this study, we report a new reductive etherification procedure for protection of carbohydrate substrates and its application for one-pot preparation of glycosyl building blocks. The reported procedure features the use of polymethylhydrosiloxane (PMHS) as a sub-stoichiometric reducing agent, which prevents the transilylation side reaction and improves the efficiency of the reductive etherification method. Application of the PMHS reductive etherification procedure for one-pot protecting manipulation are described.

Introduction

Protecting group manipulations are mandatory in chemical synthesis of oligosaccharides and related glycoconjugates, where the polyhydroxyl glycosyl substrates are properly protected for regio- and stereo-selective glycosylations.[1-4] An elegant strategy to streamline protecting group manipulation is one-pot regioselective protection and/or deprotection; in which two or more reaction steps are combined into a one-pot reaction sequence.[5-10] A key step in such one-pot protecting group manipulation is the trialkylsilane reductive etherification. In the 70s, Doyle et al. reported the reductive etherification of carbonyl compounds in alcohols using triethylsilane (Et_3SiH) as the reducing source;[11] thereafter, various related reductive etherification procedures have evolved.[12]

In a project concerning the preparation of thioglucosamine building block for synthesis of glucosamine glycans, the C-3 hydroxyl of *N*-trichloroethoxycarbonyl (Troc)-thioglucosamine **1**[13] was protected with a naphthylmethyl (Nap) protecting group via a Et_3SiH reductive etherification procedure.[14] Thus, **1** was silylated with hexamethyldisilazane (HMDS) to give a TMS protected intermediate, which was subjected the etherification at 0 °C. However, the reaction afforded a mixture of desired alkylation product **2**, transacetalation product **3**, and transilylation product **4** in 65%, 21%, and 7%, respectively (Scheme 1). Products **2** and **3** were not separable by the column chromatography.[15] The formation of transacetalation product **3** implicates the vulnerability of the benzylidene acetal. The formation of transilylation product **4** should stem from the use of Et_3SiH.[12d]

To improve the applicability of the reductive etherification procedure, we sought to search for solutions to address the aforementioned issues. Herein, we report a new reductive etherification procedure for protection of carbohydrate substrates. In the new procedure, polymethylhydrosiloxane (PMHS) is used as a sub-stoichiometric reagent, which prevents the transilylation side reaction. In development of the etherification method, we also clarified the experimental conditions that enable the suppression of the transacetalation.



Scheme 1. Transacetalation and transilylation side reactions in Et_3SiH reductive etherification of thioglucosamine **1** at 0 °C.

Results and discussion

1.1 Development of the PMHS Reductive Etherification

At first, we sought to elucidate the influence of temperature on transacetalation and transilylation under the Et_3SiH reductive etherification conditions (Table 1). Thus, substrate **1** was first converted to 3-*O*-TMS-protected thioglucosamine **1a** via the HMDS silylation. Upon completion of the silylation, the reaction was worked up to give crude TMS-protected thioglucosamine **1a**, which was used for etherification.[16] Thus, **1a** was treated with 2-naphthylaldehyde (NapCHO), Et_3SiH, and 0.1 equiv. of trimethylsilyl trifluoromethanesulfonate (TMSOTf) at −30 °C and −78 °C in accordance with literature procedures (Table 1, entries 1 and 2).[12e,14] In comparison with the reductive etherification in Scheme 1, the formation of transacetalation product **3** was greatly reduced at these sub-zero temperatures, though the formation of transilylation product **4** was enhanced. Further decreasing the reaction temperature to −86 °C impractical for TMS-protected thioglucosamine **1a** due to it poor solubility.[6,17,18] Increasing the amount of TMSOTf to 0.2 equiv. did improve the yield of the etherification, but some transilylation product **4** (~5%) still remained (entry 3).

In the literature, PMHS has been used as a hydride source for various reduction reactions,[19-21] although its applicability to glycosyl substrates has rarely been studied.[22] Hence, we were of

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Electronic Supplementary Information (ESI) available: general PMHS reductive etherification and one-pot protecting group manipulation procedure, NMR spectroscopic data of **2**–**4**, **7**–**9**, **10a**–**10k**, **12a**–**12k**, **17**, **18**, **21**, and **24** are available. See DOI: 10.1039/x0xx00000x

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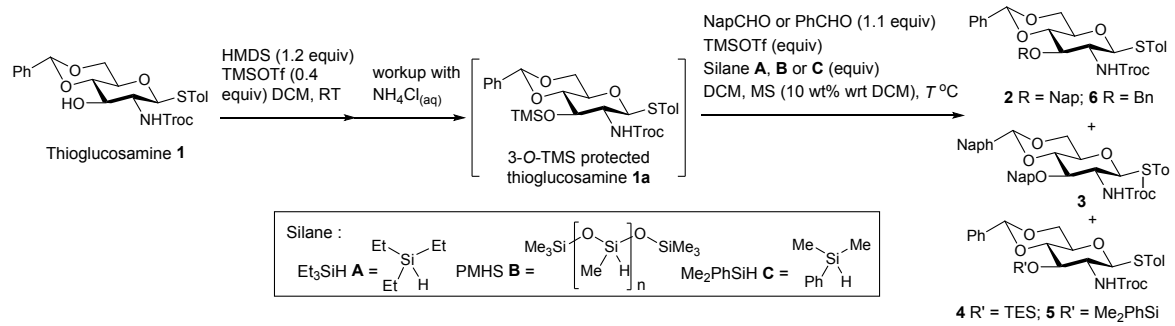
interest to explore the utility of PMHS in the reductive etherification of carbohydrate substrates. Initially, thioglucosamine **1a** was treated with 1.1 equiv. of NapCHO, 1.0 equiv. of PMHS (number average molecular weight, Mn = 1900), and 0.2 equiv. of TMSOTf at −78 °C (Entry 4). To our satisfaction, the reaction was complete in 2 h affording desired alkylation product **2** in 82% yield with no transilylation product. For comparison, the reductive etherification of **1a** was repeated with dimethylphenyl silane (Me_2PhSiH) (Entry 5), however this silane reagent was less reactive than either PMHS or Et_3SiH, and alkylation product **2** was obtained in only a moderate yield (40%), together with unreacted **1a** and transilylation product **5**.

As PMHS contains multiple hydride-donating (Si–H) groups, it is logical to reduce the stoichiometric amount of the reagent. Accordingly, the etherification of **1a** was performed with 0.5 equiv. of PMHS at −60 °C (Entry 6). Satisfyingly, this sub-stoichiometric amount of PMHS afforded an excellent yield (83%) of **2**. Further reduction of PMHS to 0.25 equiv. rendered a slower reaction and although the reaction rate could be improved by addition of 0.4 equiv. of TMSOTf or by raising the reaction temperature to −30 °C. Both of the modified procedures enhanced formation of the transacetalation product **3** (Entries 7 and 8). Nevertheless, when benzaldehyde (PhCHO) was used as the etherification reagent, a higher reaction temperature and a lower dosage of PMHS were acceptable because both of the transacetalation and reductive etherification would give the same alkylation product **6** (Entry 9). However, further reduction of PMHS to 0.15 equiv. was ineffective even a 0 °C reaction temperature was applied (Entry10). Based on the aforementioned studies, the reaction conditions for entries 6 and 9 were chosen for implementation of the PMHS reductive etherification procedure.

Table 1: Sequential Silylation and Reductive Etherification Procedure



Entry	Aldehyde (equiv.)	Silane reducing agent (equiv.)	TMSOTf (equiv.)	*T* (°C)	Time (h)	Desired product **2** or **6** (%)[a]	**2** : **3** ratio from NMR	Transilylation product (%)	Remark
1	NapCHO (1.1)	A (1.2)	0.1	–30	2	**2** (56)	96 : 4	**4**, 21	Ref 12e
2	NapCHO (1.1)	A (1.2)	0.1	–78	2	**2** (61)	97 : 3	**4**, 18	Ref 14,17
3	NapCHO (1.1)	A (1.2)	0.2	–78	2	**2** (80)	97 : 3	**4**, 5	-
4	NapCHO (1.1)	B (1.0)	0.2	–78	2	**2** (82)	97 : 3	-	-
5	NapCHO (1.1)	C (1.2)	0.2	–60	4	**2** (40)	98 : 2	**5**, 20	incomplete
6	NapCHO (1.1)	B (0.5)	0.2	–60	2	**2** (83)	97 : 3	-	-
7	NapCHO (1.1)	B (0.25)	0.4	–60	4	**2** (81)	92 : 8	-	-
8	NapCHO (1.1)	B (0.25)	0.2	–30	2	**2** (65)	77 : 23	-	-
9	PhCHO (1.1)	B (0.25)	0.2	–30	2	**6** (83)	-	-	-
10	PhCHO (1.1)	B (0.15)	0.2	0	2	**6** (65)	-	-	-

[a] Yields of **2** from entries 1-8 were derived from the ratio of **2** and **3** in proton NMR spectrum.

To gain insight to the mechanistic aspect of the transacetalation reaction, 4,6-*O*-benzylidene protected *N*-Troc thioglucosamine **6** was treated 0.1 equiv. of TMSOTf in the absence or presence of NapCHO (Schemes 2a and 2b). In the absence of NapCHO, *ca.* 50% of thioglucosamine **6** underwent debenzylidenation to give thioglucosamine diol **7** (Scheme 2a). Of note, the anomeric configuration of thioglucosamine **6** and diol **7** was stable throughout the course of the reaction. Interestingly, in the presence of NapCHO, a 3:2 inseparable mixture of transacetalation product **8** and thioglucosamine substrate **6** was obtained (Scheme 2b).

Based on the reactions in Schemes 2a and 2b, the transacetalation is likely attributed to a consecutive debenzylidenation and acetal formation process. Thus, we hypothesized that if the arylidene group of the transacetalation product is more stable than that of the starting substrate, then the transacetalation would prevail. For validation, we repeated the transacetalation experiment with *p*-nitrobenzaldehyde (pNO_2PhCHO) (Scheme 2c). After 18 h, ~ 90% of the benzylidene group of **6** was replaced with pNO_2PhCHO to give transacetalation product **9**, which presumably acquired a more stable acetal group. Notably, product **9** existed as a pair diastereomers, which were characterized by a pair arylidene proton signals at 5.62 and 6.14 ppm in ~ 5.7:1 *R*:*S* ratio (assignment supported by 1D and 2D NMR spectra, see SI). Similar to the reactions in schemes 2a and 2b, no sign of anomerization was observed.

1.2 Scope and Limitations of the PMHS Reductive Etherification

With the PMHS reductive etherification procedure in hands, we explored its substrate scope and limitations. To this end, a series of polyol substrates (**10a**–**c**) and glycoside substrates (**10d**–**k**)

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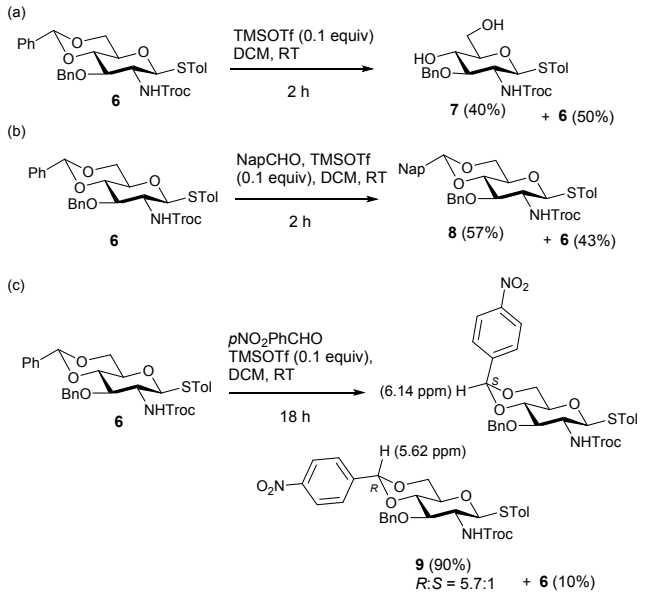


Scheme 2. (a) Treatment of **6** with TMSOf alone. (b) Treatment of **6** with TMSOTf in the presence of NapCHO. (c) Treatment of **6** with TMSOTf in the presence of *p*NO_2PhCHO.

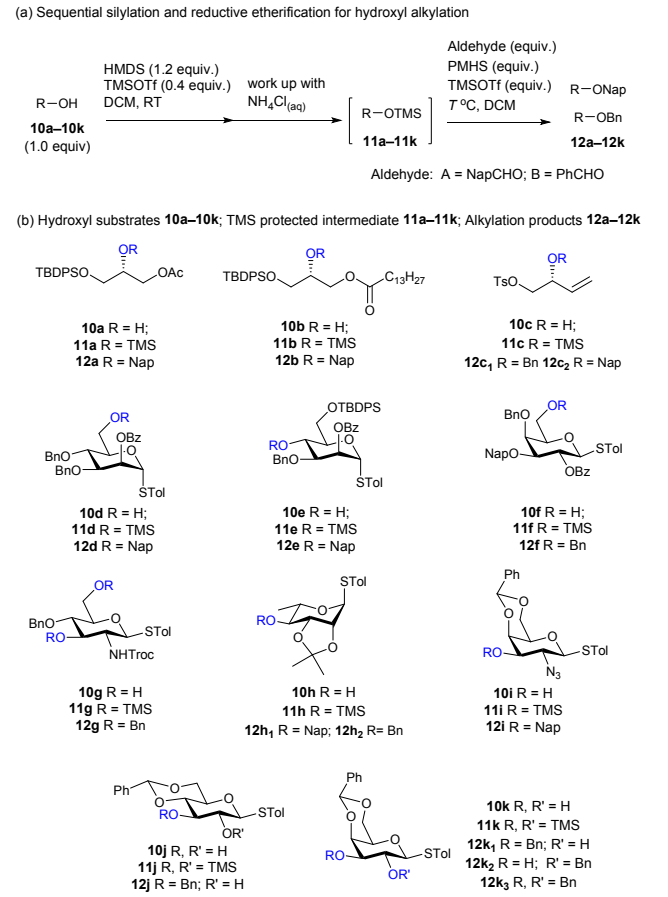
were subjected to the sequential silylation and PMHS reductive etherification protocol (Scheme 3, Table 2). Substrates **10a**–**10g** contain various basic-labile protecting groups that may undergo hydrolysis and/or migration in Williamson alkylation conditions. In addition, it was necessary to probe the suitability of the etherification procedure for some representative benzylidene or isopropylidene protected substrates **10h**–**10k**.

In the general protocol, substrate **10** was treated with HMDS to give TMS protected intermediate **11**. After removing the residual HMDS and its byproducts by the aqueous workup, crude intermediate **11** was etherified with 1.1 equiv. of NapCHO (or PhCHO) and 0.25 or 0.5 equiv. of PMHS at –20 to –70 °C in the presence of TMSOTf. Nevertheless, for particular substrates, the amount of TMSOTf had to be optimized.

The sequential silylation and PMHS reductive etherification of 1-acetyl-3-TBDP *sn*-glycerol **10a** with NapCHO proceeded smoothly to give desired alkylation product **12a** yield via silylated intermediate **11a** (Table 2, entry 1). In the reaction conditions, no acetyl group migration was observed and the overall yield of **12a** was 83%. As for comparison, the Et_3SiH reductive etherification of **11a** was repeated with 0.1 and 0.2 equiv. of TMSOTf (Entries 2 and 3). The yields of the reactions were lower than that given by the PMHS reductive etherification due to the formation of bis(naphthylmethyl) ether $[(Nap)_2O]$.[23] Gratifyingly, such a side product was not observed for the PMHS reductive etherification of **11a**.[24]

The reductive etherification was sensitive to steric factors. This was evidenced by the silylation and PMHS reductive etherification of 1-myristoyl-3-TBDP *sn*-glycerol **10b**, whereas, the yield of the reaction was just 42%. (Entry 4). Alkylation of alkenyl substrate **10c** is difficult in basic conditions due to the competition of the epoxidation. However, with the PMHS reductive etherification method, **11c** could be alkylated with either NapCHO or PhCHO to give desired products **12c$_1$** or **12c$_2$** in reasonably yields (Entries 5 and 6).

After examining the polyol substrates **10a**–**10c**, we examined the sequential silylation and reductive etherification of carbohydrate substrates **10d**–**10g**, which contained both primary and secondary hydroxyl groups (Entries 7–10). Regardless the position of the hydroxyl group, the silylation and reductive etherification was fine and desired alkylation products **12d**–**12g** were acquired in reasonable yields (70–78%). A higher (–20 °C) reaction temperature was required for reductive etherification of **11e** due to a hindered C4 hydroxyl group (Entry 8). For cyclic arylidene or alkylidene protected substrates **10h**–**10k**, some optimization at reaction temperature and amount of the TMSOTf catalyst were required to prevent the transacetalation. Thus, the silylation and PMHS reductive etherification of 2,3-*O*-isopropylidene-thio-L-rhamnoside **10h** with NapCHO and PhCHO gave desired alkylation products **12h$_1$** and **12h$_2$** in 72% and 88% yields, respectively, demonstrating that the dixolane-type acetal protection was stable in present etherification conditions (Entries 11 and 12). As for comparison, the reductive etherification of **11h** was repeated with Et_3SiH (Entry 13). The reaction gave desired product **12h$_2$** in 60% yield, together with~10% transilylation product. For sequential silylation and reductive etherification of 2-azido-2-deoxy-thiogalactosamine **10i** with NapCHO, a lower (–70 °C) reaction temperature was



Scheme 3. Sequential silylation and reductive etherification of substrates **10a**–**10k**.

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Table 2: Scope and limitations of sequential silylation and PMHS-mediated reductive etherification procedure

Entry	Substrate	RCHO (equiv.)	Silane (equiv.)	TMSOTf (equiv.)	*T* (°C)	Product (%)
1	**10a**	NapCHO (1.1)	PMHS (0.25)	0.2	–30	**12a** (83)
2	**10a**	NapCHO (1.1)	Et_3SiH (1.2)	0.1	–30	**12a** (62)[a]
3	**10a**	NapCHO (1.1)	Et_3SiH (1.2)	0.2	–30	**12a** (77)[b]
4	**10b**	NapCHO (1.5)	PMHS (0.25)	0.2	–30	**12b** (42)
5	**10c**	PhCHO (1.1)	PMHS (0.25)	0.1	–30	**12c$_1$** (78)
6	**10c**	NapCHO (1.1)	PMHS (0.25)	0.2	–30	**12c$_2$** (86)
7	**10d**	NapCHO (1.1)	PMHS (0.5)	0.1	–30	**12d** (78)
8	**10e**	NapCHO (1.1)	PMHS (0.25)	0.2	–20	**12e** (73)
9	**10f**	NapCHO (1.1)	PMHS (0.25)	0.1	–30	**12f** (75)
10	**10g**	PhCHO (1.1)	PMHS (0.25)	0.2	–30	**12g** (70)[d]
11	**10h**	NapCHO (1.1)	PMHS (0.25)	0.1	–30	**12h$_1$** (72)
12	**10h**	PhCHO (1.1)	PMHS (0.25)	0.1	–30	**12h$_2$** (88)
13	**10h**	PhCHO (1.1)	Et_3SiH (1.2)	0.2	–30	**12h$_2$** (60)[c]
14	**10i**	NapCHO (1.1)	PMHS (0.5)	0.2	–70	No reaction
15	**10i**	NapCHO (1.1)	PMHS (0.5)	1.0	–70	**12i** (85)
16	**10j**	PhCHO (1.1)	PMHS (0.25)	0.1	–30	**12j** (70)[d]
17	**10k**	PhCHO (1.1)	PMHS (0.5)	0.6	–70	**12k$_1$**, **12k$_2$**, **12k$_3$** (73)[d]

[a]3% $(Nap)_2O$ was obtained. [b]10% $(Nap)_2O$ ether was obtained. [c] 5% Transilylation product was isolated. [d] THF was used as a solvent for HMDS-based silylation. [e] Ratio of **12k$_1$**, **12k$_2$**, and **12k$_3$** = 3:5:1.

applied to prevent the transacetalation (Entry 14). However, the reaction did not proceed in the presence of 0.2 equiv. of TMSOTf. This might be attributable to the inherent basicity of the azido group, which would attenuate the catalytic ability of TMSOTf.[25-27] After some experimentations, 1.0 equiv. of TMSOTf was found effective for triggering the reaction (Entry 15). As such, desired alkylation product **12i** was obtained in 85% yield. Interestingly, no sign of the transacetalation occurred for **12i** in such acidic conditions, which may be attributable to the lower reaction temperature.

In previous studies, the etherification of a 2,3-di-*O*-TMS protected glucoside gave a C3 alkylation product in excellent regioselectivity.[7,14] It was thus of interest to determine whether our new etherification method exhibited similar selectivity. Thus, **10j** was taken to silylation to give 2,3-di-*O*-TMS thioglucoside **11j**. Subsequent PMHS reductive etherification of thioglucoside **11j** with 1.1 equiv. of PhCHO at –30 °C afforded 3-*O*-Bn protected thioglucoside **12j** in 70% yield as the sole isomer with no 2-*O*-alkylation and 2,3-*O*-dialkylation products. However, similar regioselectivity was not observed for thiogalactosyl substrate **10k** that containing a D-*galacto* skeleton (Entry 17). The reaction resulted in a mixture of 3-*O*-alkylation **12k$_1$**, 2-*O*-alkylation **12k$_2$**, and dialkylation **12k$_3$** products in a 3:5:1 ratio.[28]

1.3 Sequential Silylation and One-Pot Protection Group Manipulation

Based on the PMHS reductive etherification method, we developed the one-pot protecting-group manipulation protocols for unprotected thioglycoside substrates **13**,[29] **14**,[30] and **15** (Schemes 4a–4c).[31] To simplify the procedure and avoid the need to purify the TMS glycosyl substrate, the silylation step was coupled with the one-pot protecting-group manipulation via a workup procedure.

Scheme 4a depicts the sequential silylation and one-pot preparation of 6-hydroxyl and 4-hydroxyl *N*-Troc protected thioglucosamine acceptors **17** and **18** from *N*-Troc thioglucosamine **13**. The reaction commenced with the silylation of **13** in THF to give *per*-*O*-TMS protected thioglucosamine **16**, which was the feedstock for one-pot protecting group manipulation. The one-pot reaction started with the benzylidenation of **16** with PhCHO to give benzylidene protected thioglucosamine **1a**, which was subjected to the PMHS reductive etherification with a supplementary dose of PhCHO and 0.25 equiv. of PMHS to give benzylated product **6**. The one-pot benzylidenation and reductive etherification was performed at –30 °C. Subsequent reductive cleavage of the benzylidene group of **6** was envisaged to enable the access of 6-hydroxyl acceptor **17** or 4-hydroxyl acceptor **18**. Thus, treatment of **6** with borane-THF (BH_3.THF) and TMSOTf furnished 6-hydroxyl acceptor **17**.[32] On the other hand, treatment of **6** with Et_3SiH and trifluoroacetic acid (TFA) –20 °C acquired 4-hydroxyl acceptor **18**.[33,34] The overall yields for **17** and **18** over 4 reaction steps are 45% and 50%, respectively. In the previous one-pot preparation of **18**, the overall yield was 33%.[18]

Next, we examined the preparation of 2-azido-2-deoxy-thiogalactosamine acceptor **21** from unprotected 2-azido-2-deoxythiogalactosamine **14** based on the silylation and one-pot protecting group manipulation strategy (Scheme 4b). Thus, 2-azido-thiogalactosamine **14** was subjected to the HMDS silylation to give *per*-*O*-TMS protected 2-azido-2-deoxythiogalactosamine **19**. After the workup, crude intermediate **19** was reacted with PhCHO at −30 °C to give

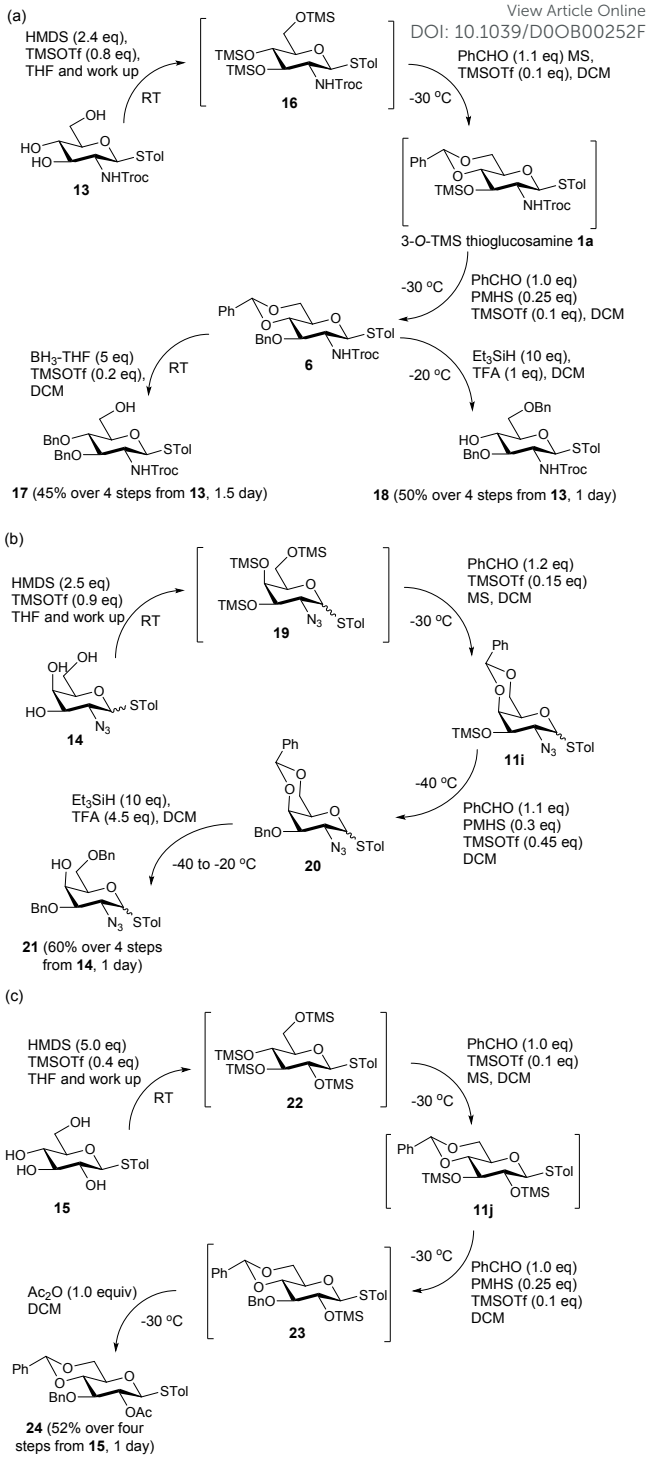
benzylidene intermediate **11i**. Subsequent PMHS reductive etherification of **11i** with a supplementary dose of PhCHO and 0.3 equiv. of PMHS furnished 2-azido-3-*O*-benzyl-4,6-*O*-benzylidene-thiogalactoside **20**. Unlike the above reductive etherification of **11i** with NapCHO in entry 15 of Table 2, a higher (–40 °C) temperature was allowed for the reductive etherification with PhCHO because the latter would not suffer from the transacetalation. Reductive acetal cleavage of **20** with Et_3SiH and TFA completed the preparation of 4-hydroxyl acceptor **21** in good 60% overall yield (4 steps from **14**).

After the one-pot preparation of glycosamine acceptors **17**, **18**, and **21**, the sequential silylation and one-pot protecting group manipulation protocol was applied for preparation of thioglucoside donor **24** from unprotected thioglucoside **15** (Scheme 4c). Thus, the HMDS-based silylation of unprotected thioglucoside **15** afforded *per*-*O*-TMS-protected thioglucoside **22**. In contrast to the silylation of substrates **13** and **14**, a large excess of HMDS (5 equiv.) was required to effect the conversion of **15** to **22**. We also note that the C2 hydroxyl of thioglucoside **15** was much less reactive than the C3 and C4 hydroxyls in silylation. Subsequent benzylidenation of **22** with PhCHO at –30 °C afforded benzylidene intermediate **11j**, which was subjected to the PMHS reductive etherification with a supplementary amount of PhCHO at –30 °C to produce alkylation product **23**. Final acetylation of **23** with acetic anhydride (Ac_2O) furnished desired thioglucosyl donor **24** in 52% yield (over 4 reaction steps from **15**). In the previous one-pot protocol, this acetylation was a two-step process, comprising a desilylation and base-promoted acetylation.[17]

In above one-pot reactions, the TMS protected intermediates were not stable in acidic conditions; and thus, they may have been partially hydrolysis in the TLC plate. Therefore, in monitoring the progress of the one-pot reaction by TLC, some rationalization was required in result interpretation.

Conclusions

In summary, we have developed a new reductive etherification procedure for carbohydrate substrates. The new procedure uses polymethylhydrosiloxane (PMHS) as a sub-stoichiometric reducing agent, which prevents the transilylation side reaction. Based on the PMHS reductive etherification procedure, several sequential silylation and one-pot protecting group manipulation protocols have been developed. In addition to the method development, we clarified the causes of the transacetalation side reaction that occurred during the etherification of cyclic acetal protected glycosyl substrates. This information will be useful when using the silane based reductive etherification procedure to protect the polyol substrates.



Scheme 4. One-pot protecting group manipulation of (a) unprotected *N*-Troc-thioglucosamine **13**, (b) 2-azido-2-deoxy-thiogalactoside **14**, and (c) thioglucoside **15**

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

‡ Supporting information for general PMHS reductive etherification and one-pot protecting group manipulation procedure, NMR spectroscopic data of **2**–**4**, **7**–**9**, **10a**–**10k**, **12a**–**12k**, **17**, **18**, **21**, and **24** are available.

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16 In previous protocol, the basic HMDS by-products were removed by purging with N_2, but we found that the workup procedure (washing $NH_4Cl_{(aq)}$) was more reliable for removal of the by-products, which if present might affect the acid-catalyzed etherification.
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