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Chemoselective per-*O*-trimethylsilylation and homogeneous *N*-functionalisation of amino sugars†

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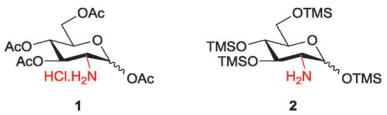
A highly efficient CH_3CN-promoted hexamethyldisilazane per-*O*-trimethylsilylation of amino sugars was developed. Its applications in homogenous *N*-functionalisation and a concise synthesis of glucosamine 6-phosphate are described.

Amino sugars are widely dispersed in nature and have been found in numerous biologically potent polysaccharides such as mucopolysaccharides or mucoproteins, bacterial capsular polysaccharides, lipopolysaccharides, glycolipids, *N*-glycans, glycosaminoglycans, and numerous antibiotics.[1,2] More than 60 amino sugars are known, and amongst them, D-glucosamine and its *N*-acetylated and -sulfonated derivatives are commonly found in bioactive molecules.[2] Therefore, amino group functionalisation is one of the most fundamental modifications when dealing with amino sugars, but the current methods are laborious. Efforts have been made to functionalise the amino groups in the presence of multiple hydroxyl groups of sugar molecules. Amine groups can be chemoselectively functionalised in the presence of multiple hydroxyl groups by using the reactivity differences in nucleophilicity under the Schotten–Baumann conditions (acid chloride and aqueous $NaHCO_3$); however, this method requires an excessive number of reagents. Moreover, isolating products from aqueous media and salts is often difficult and time consuming. In many cases, reverse-phase chromatography or per-*O*-acetylation of the product after the reactions are occasionally required because of the high polarity of desired molecules, but the yields are usually only moderate. Therefore, upscaling these reactions is often difficult even though it is often the first step in the synthesis process.[3] To enable homogeneous *N*-functionalisation of glucosamine, per-*O*-acetylated glucosamine hydrochloride **1**,[4] which requires three steps to prepare, is usually used as an alternative.[5] Hence, to produce these functionalised amino sugars on a large scale, an efficient, simple, economic, and reliable method is still required (Scheme 1).



Scheme 1 Per-*O*-functionalised glucosamine derivatives.

Because solubility is the key concern in the synthesis of amino sugar derivatives, we propose chemoselective masking of all hydroxyl groups over the amine group to enable subsequent amine modification as an efficient solution to the aforementioned problems. Therefore, we expected that per-*O*-trimethylsilylated glucosamine **2** would satisfy the requirements. Although **2**[6] and its triethylsilyl derivatives have been prepared and Boysen *et al.* used them to prepare Glucobox derivatives,[7] the existing method to prepare them needs a large excess of silylating reagents, including TMSCl (10 eq.), hexamethyldisilazane (HMDS) (10 eq.) and bis-(trimethylsilyl)acetamide (BSA) (1 eq.), and a longer reaction time. Difficult workup and additional purifications are required to remove the extra reagents, the *N*-trimethylsilylated derivative and salts, giving lower yield.[6] The applications of **2** have neither been studied extensively nor extended, probably because it is difficult to prepare.

Per-*O*-trimethylsilyl derivatives of carbohydrates have been applied widely in the preparation of building blocks for oligosaccharide synthesis.[8] We recently developed a highly efficient TMSOTf-catalysed HMDS silylation of carbohydrates.[9] Although nitromethane-promoted HMDS silylation of alcohols was reported,[10] no effective solvent-promoted HMDS trimethylsilylation of amino sugars has been described. Here, we report that glucosamine hydrochloride (**3**) can be treated with 2.5 equivalents of HMDS in acetonitrile for 3 h at room temperature under catalyst-free conditions to yield **2** as a single α-isomer in a nearly quantitative yield after simply filtering and

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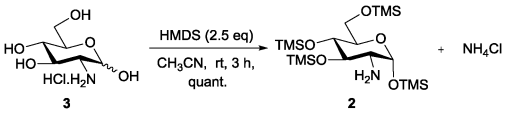


3 2

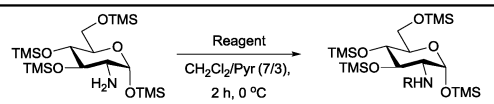
Scheme 2 CH_3CN-promoted chemoselective silylation of glucosamine hydrochloride (**3**).

evaporating acetonitrile (Scheme 2), and the reaction can be easily scaled up to a 25 g scale (see ESI†). Therefore, the hydroxyl groups of an amino sugar can be masked efficiently and easily with the amine groups unaffected by taking advantage of the stronger bond dissociation energy of O–Si compared with that of the N–Si bond.

In addition, our method involves using a minimal amount of reagents and enables amine protection or functionalisation reactions after simple filtration and evaporation. Because the amino group remains intact, we screened various *N*-functionalisation for **2** by using various amine protecting groups in CH_2Cl_2/Pyr (7/3) at 0 °C to produce compounds **4–15** with 75% to 95% yields as summarised in Table 1.

Azide is amongst the few neighbouring nonparticipating amine protecting groups and is essential for 1,2-*cis* glycosylation reactions of 2-amino glycosides.[3b,11] The diazotransfer reactions of amino glycosides traditionally begin with direct amine functionalisation of amino sugars under heterogeneous H_2O/CH_2Cl_2 biphase conditions, and, thus, vigorous stirring and a long reaction time are required. Furthermore, the arduous workup and purification processes require large quantities of solvents and eluents. Although further acetylation[11a,c] or silylation[11d] of the crude products can facilitate purification, these treatments are also inefficient and require an excessive number of reagents. By contrast, we per-*O*-trimethylsilylated the amino sugars first, thus, the diazotransfer reactions could be conducted under homogeneous conditions with TfN_3 and DMAP in CH_2Cl_2 (Table 2).[12] Considering D-glucosamine (**3**) as an example (entry 1), the reaction was completed within 12 h, and, without workup and extraction,

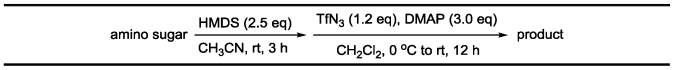
Table 1 *N*-Functionalisation of compound **2** with various protecting groups

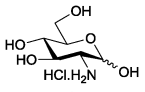
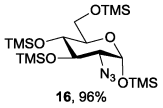
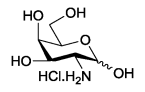
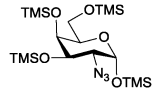
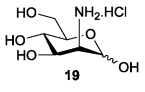
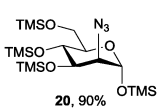


2 4-15

Entry	Reagent	R (product)	Yield (%)
1	TCACl	TCA (**4**)	87
2	Ac_2O	Ac (**5**)	77
3	TFAA	TFA (**6**)	88
4	TrocCl	Troc (**7**)	91
5	CbzCl	Cbz (**8**)	81
6	MsCl	Ms (**9**)	85
7	TsCl	Ts (**10**)	75
8	DNSCl	DNS (**11**)	89
9	Benzenesulfonyl chloride	Benzenesulfonyl (**12**)	78
10	*p*-Nitro-benzenesulfonyl chloride	*p*-Nitrobenzenesulfonyl (**13**)	77
11	2,4-Dinitrobenzenesulfonyl chloride	2,4-Dinitrobenzenesulfonyl (**14**)	78
12	Lauoryl chloride	Lauoryl (**15**)	86

Table 2 Chemoselective silylation followed by diazotransfer reaction of amino sugars

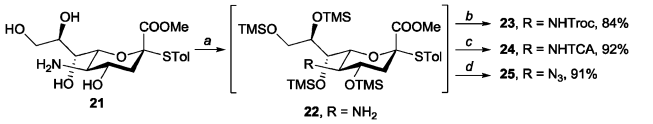


Entry	Amino sugar	Product
1	 **3**	 **16**, 96%
2	 **17**	 **18**, 91%
3	 **19**	 **20**, 90%

product **16** was obtained easily by evaporation and simple filtration through a short pad of silica gel to give 96% yield of **16** as a single α-anomer. Similarly, by using the same reaction conditions and starting from D-galacto- (**17**) and D-mannosamine (**19**) (entries 2 and 3), the corresponding azide products **18** and **20** were obtained in 91% and 90% yields, respectively, as single α-anomers. With the amino group functionalised, the *O*-trimethylsilyl groups can be easily removed or further utilized for other functional group modifications.[8,9]

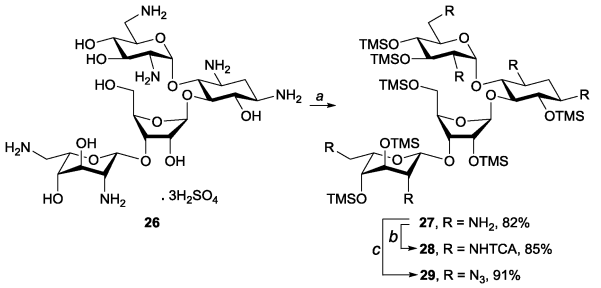
Based on these results, we extended our method to sialic acid. Specifically, we applied our method to the sialic acid derivative **21**[13] to prepare sialic acid donors with various *N*-functional groups, which play crucial roles in the stereoselectivity of sialylation reactions.[14] The chemoselective HMDS silylation of **21** yielded **22** quantitatively, and then amine functionalisation was performed in the same pot. Sialic acid derivatives with *C*5 NHTroc (**23**), NHTCA (**24**), and N_3 (**25**) were easily obtained in 84%, 92%, and 91% yields, respectively (Scheme 3).

To test the applicability of our method to molecules containing multiple amine groups, we applied our method to neomycin sulphate (**26**). Because of the poor solubility of **26**, the chemoselective per-*O*-silylation required a longer reaction time (36 h) and more HMDS (7.0 eq.) as compared to the previous examples. However, the pure product **27** was obtained after simple filtration and solvent evaporation in an 82% yield. Compound **27** was subjected to amine functionalisation reactions, which yielded per-*N*-trichloroacetylated **28** and per-*N*-azidated **29** in 85% and 91% yield, respectively (Scheme 4).

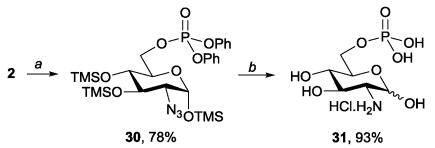


21 22, R = NH_2

Scheme 3 Chemoselective amine functionalisation of the sialic acid derivative. *Reagents and conditions*: [a] HMDS (3.0 eq.), CH_3CN, rt, 3 h. [b] TrocCl (1.1 eq.), CH_2Cl_2/Pyr (7/3), 0 °C to rt, 2 h. [c] TCACl (1.1 eq.), Pyr/CH_2Cl_2 (7/3), 0 °C to rt, 2 h. [d] TfN_3 (1.1 eq.), DMAP (3.0 eq.), CH_2Cl_2, 0 °C to rt, 12 h.



Scheme 4 Chemoselective per-*O*-trimethylsilylation and amine functionalisation of neomycin sulphate (**26**). *Reagents and conditions*: [a] HMDS (7.0 eq.), CH_3CN, rt, 36 h. [b] TCACl (7.0 eq.), CH_2Cl_2/Pyr (7/3), rt, 2 h. [c] TfN_3 (10.0 eq.), DMAP (18.0 eq.), CH_2Cl_2, rt, 5 h.



Scheme 5 Concise synthesis of glucosamine 6-phosphate. *Reagents and conditions*: [a] TfN_3 (1.2 eq.), DMAP (3.0 eq.), CH_2Cl_2, 0 °C to rt, 12 h; then in one-pot, $(PhO)_2POCl$ (3.0 eq.), Pyr, 0 °C to rt, 6 h. [b] H_2, $Pd(OH)_2$, 75% $EtOH_{(aq.)}$, 16 h; then 1 M $HCl_{(aq.)}$, 2 h; then H_2, PtO_2, 75% $EtOH_{(aq.)}$, 10 h.

Glucosamine 6-phosphate (**31**) has recently received substantial attention because of its potent biological activity in ribosomal cleavage.[6c,15] Although some chemical[16a,b] and enzymatic syntheses have been reported in recent years,[6c,16c] there is still room for an efficient chemical synthesis. The concise and efficient synthesis of **31** from **2** was achieved using our method, producing an overall yield of 73%. As shown in Scheme 5, per-*O*-trimethylsilylated glucosamine (**2**) was first treated with TfN_3 and DMAP to conduct a diazotransfer reaction. The homogeneous conditions then enabled a *C*6 phosphorylation reaction to be conducted in a one-pot manner. Thus, pyridine and $(PhO)_2POCl$ were added subsequently. The glucosamine 6-phosphate derivative **30** was isolated in a 78% yield by using our recently reported method.[9b] Reducing the azide group of **30**, neutralising the amine group with $HCl_{(aq.)}$, and hydrogenolysing the diphenyphosphate group yielded glucosamine 6-phosphate **30** in a 93% yield.

In conclusion, we reported a simple, efficient and consistent method for preparation of per-*O*-trimethylsilylated amino sugars with unprotected amines. In addition, various homogeneous chemoselective *N*-functionalisations, which have much improved procedures as compared to the traditional methods, especially the *N*-azidation, were achieved. Our method was effective for both mono and multiple amine substrates. Moreover, we synthesised glucosamine 6-phosphate efficiently. We believe that this method has simplified and advanced the preparation of carbohydrate building blocks containing amino groups, especially on a large scale, and will facilitate the synthesis of carbohydrate molecules containing amino sugars.

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