Highly Efficient Synthesis of Oligo-*N*-acetylglucosamines by Iterative Glycosylation of Di- and Tetrachlorophthaloyl-protected Thioglucosamines

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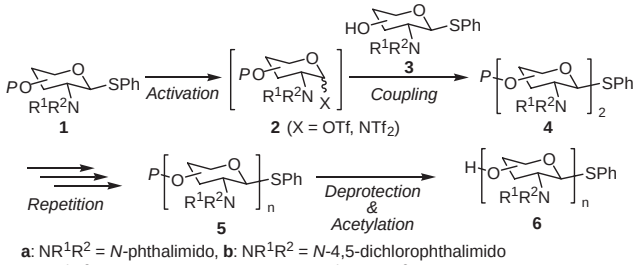
The iterative glycosylation of di- and tetrachlorophthaloyl-protected thioglucosamines, which act as both glycosyl donors and acceptors, gives the corresponding protected oligoglucosamines. Subsequent removal of the protecting groups followed by acetylation of the free amines affords oligo-*N*-acetylglucosamines in good to excellent combined yields.

2-Deoxy-2-*N*-acetylaminoglycosides are major components of many biologically active oligosaccharides.[1] Therefore, the development of an efficient method to construct oligosaccharides that contain 2-deoxy-2-*N*-acetylglucosamines is currently one of the most important goals in synthetic carbohydrate chemistry.[2,3]

We have recently reported an iterative method to synthesize *N*-phthalimido (Phth)-protected oligo(2-deoxy-2-aminoglycosides) from the corresponding thioglycosides, which acted as both glycosyl donors and acceptors (**1a** and **3a** in Scheme 1).[4] This method involves the activation of **1a** to give the α-glycosyl triflate or the β-glycosyl triflimide intermediate **2a**, which subsequently couples with **3a** to give the disaccharide **4a** in high yield. Since **4a** is also a thioglycoside, iteration of the same reaction sequence results in the formation of the oligoglycoside **5a**. However, despite the high efficiency of the coupling sequence, complete deprotection of the Phth-group was not achieved in many cases, especially when the number of sugar units was large.[2] The inefficiency of this deprotection step led to difficulties in isolating the final acetylated product **6d** from the complex reaction mixtures. These results prompted us to investigate alternative *N*-protecting groups, which must be compatible with the iterative glycosylation and must then allow deprotection in high yield.

We focused on thioglucosamines possessing 4,5-dichlorophthalimido (DCP)[5] and tetrachlorophthalimido (TCP)[6] protecting groups (**1b** and **1c**), which are well known to be more amenable to deprotection than the Phth-group.[2b]

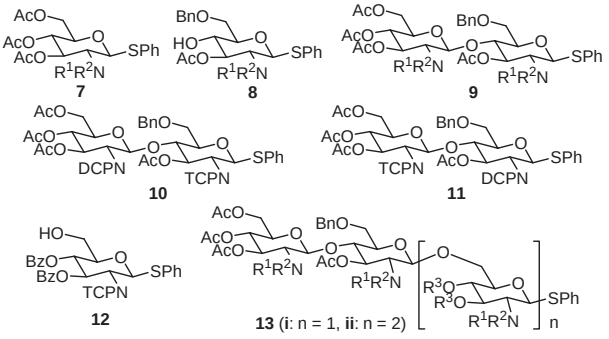
Conversely, as these groups are highly electron-withdrawing in character, we were concerned that their presence at the C-2 position in glucosamines might destabilize the cationic intermediate **2**[7] and decrease the reactivity of acceptor **3**,[8] leading to a decrease in the efficiency of the iterative process. However, we report here that the DCP- and TCP-protected thioglucosamines served as excellent glycosyl donors and acceptors. The high deprotection efficiencies of these groups thus provide an improved protocol for the synthesis of oligosaccharides containing 2-deoxy-2-*N*-acetylaminoglycosides.



a: NR^1R^2 = *N*-phthalimido, **b**: NR^1R^2 = *N*-4,5-dichlorophthalimido
c: NR^1R^2 = *N*-tetrachlorophthalimido, **d**: R^1 = Ac, R^2 = H

Scheme 1. Iterative glycosylation with thioglucosamines.

Table 1. Glycosylation and deprotection of TCP- and DCP-protected 2-deoxy-2-aminoglycoside derivatives



e: R^1,R^2 = TCP, R^3 =Bz, **f**: R^1, R^3 = Ac, R^2 = H

	Glycosylation[a]				Deprotection[b]	
Run	Donor	Acceptor	Product	Yield/%	Product	Yield/%
1	**7b**	**8b**	**9b**	85	**9d**	92
2	**7b**	**8c**	**10**	81	**9d**	99
3	**7c**	**8b**	**11**	77	**9d**	90
4	**7c**	**8c**	**9c**	75	**9d**	99
5	**9c**	**12**	**13i-e**	73	**13i-f**	98[c]
6	**13i-e**	**12**	**13ii-e**	41	**13ii-f**	96[c]

[a]Donor (1.0 equiv.), BSP (1.1 equiv.), DTBMP (2.0 equiv.), Tf_2O (1.4 equiv.), MS 4A, CH_2Cl_2, $-60\,^\circ C$, 10–30 min, then acceptor (1.5 equiv.), $-60\,^\circ C$, 15–60 min. [b]Substrate (1.0 equiv.), ethylenediamine (EA, 5.0 equiv.), MeCN/THF/MeOH (2:1:1), $60\,^\circ C$, 12–18 h, then Ac_2O (ca. 1000 equiv.), pyridine (ca. 1000 equiv.), and DMAP (ca. 1.0 equiv.). [c]Hydrazine monohydrate (50–150 equiv.) was used instead of ethylenediamine. BSP = 1-benzenesulfinyl piperidine. DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine.

We first examined the glycosylation of the candidate thioglucosamines with methanol in order to estimate the stability and reactivity of the intermediates **2b** and **2c**. The TCP-protected thioglucosamine **7c** was activated under Crich's conditions,[9] and the resulting triflate intermediate was treated with methanol (1.5 equiv.) to give the desired methyl β-*O*-glycoside in 79% yield. The analogous reaction using the DCP-protected thioglucos-

amine **7b** afforded the same β-*O*-glycoside in 77% yield. The glycosylation proceeded with complete β-selectivity in either case. The outcome of these reactions was virtually identical to that for the Phth-protected **7a** (84% yield, complete β-selectivity). Therefore, the DCP and TCP groups do not have a detrimental effect on the triflate intermediates.

We also examined the glycosylation of thioglycoside donors **7** possessing acetyl (R^1 = Ac, R^2 = H),[10] diacetyl (R^1, R^2 = Ac),[11] trichloroacetyl (R^1 = $COCCl_3$, R^2 = H),[12] and 2,2,2-trichloroethoxycarbonyl (R^1 = $CO_2CH_2CCl_3$, R^2 = H) groups.[13] However, the coupling efficiencies were low in all cases (maximum yield 7%) due to the formation of the corresponding 1,2-oxazoline and 1,2-ortho-acid derivative.[2,14]

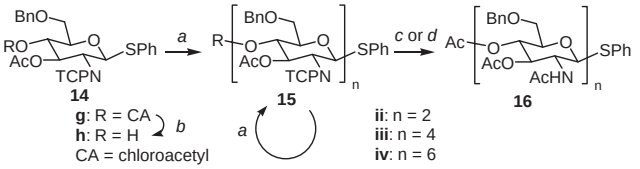
We next examined the use of the DCP- and TCP-protected thioglucosamines as glycosyl acceptors.[15] The glycosylation of **7b** with **8b** and **8c** proceeded smoothly to give the desired disaccharides **9b** and **10** in 85 and 81% yields, respectively (Table 1, Entries 1 and 2). The coupling of **7c** with **8b** and **8c** also proceeded efficiently to give **11** and **9c**, respectively, in high yields (Entries 3 and 4). These coupling efficiencies are identical to the values achieved with the Phth-protected derivatives (84% yield).[4a]

As expected, deprotection of the disaccharides **9b**, **9c**, **10**, and **11** proceeded smoothly to give **9d** in almost quantitative yields after acetylation of the resulting free amino-group (Table 1, Entries 1–4). This step was carried out by treating the disaccharides with excess ethylenediamine (EA, 5 equiv.) in a mixture of methanol, acetonitrile, and THF (2:1:1) at 60 °C for 12–18 h, followed by acetylation. Monitoring the reactions indicated that the reactivities of TCP and DCP were almost identical. Therefore, selective deprotection was thus far not achieved.

We also examined the elongation of the glucosamine unit using TCP-protected 6-hydroxy thioglycoside **12** as a glycosyl acceptor. The coupling of **9c** with **12** under identical reaction conditions afforded the trisaccharide **13i-e**, which was further coupled with **12** to give the tetrasaccharide **13ii-e**. Deprotection of **13i-e** and **13ii-e** proceeded smoothly upon treatment with hydrazine monohydrate (50–150 equiv.) at 60 °C, and the subsequent acetylation gave **13i-f** and **13ii-f**, respectively, in quantitative yields (Table 1, Entries 5 and 6). The success of this step is in contrast to the attempted deprotection of structurally similar Phth-protected tetraglucosamine containing β-1,4-linkages; yields of only 50% were achieved and inseparable mixtures of partially deprotected products were obtained under the similar reaction conditions (150 equiv. of hydrazine monohydrate, 60 °C, 80 h).

As a consequence of the above results, we were able to develop the iterative glycosylation process to synthesize oligoglucosamines consisting solely of β-1,4-linkages, using the thioglycoside **14** as a common starting substrate (Scheme 2). The glycosylation of **14g** and **14h** afforded the disaccharide **15ii-g** in 73% yield. Subsequent coupling of **15ii-g** and **15ii-h**, which was easily prepared from **15ii-g**, afforded the tetraglucosamine **15iii-g** in 81% yield. This was further reacted with **15ii-h** to give the hexasaccharide **15iv-g** in 51% yield.

Deprotection of the TCP- and chloroacetyl (CA) groups of **15ii-g** and **15iii-g** followed by acetylation gave the per-*N*-acetylated oligoglucosamines **16ii** and **16iii** in good yields. Deprotection of the hexasaccharide **15iv-g** was initially unsuccessful, but



[a]See the legend of Table 1[a], **15ii-g**; 73%, **15iii-g**; 81%, **15iv-g**; 51%. [b]Thiourea (5.0 equiv.), MeOH/CH_2Cl_2 (1:1), rt, 5 h, **15ii-h**; 100%. [c]EA (30–100 equiv.), MeCN/THF/MeOH (2:1:1), 60 °C, 12–24 h., then Ac_2O, pyridine, and DMAP, **16ii**; 90%, **16iii**; 81%. [d]EA (100 equiv.), MeOH, 120 °C, 30 min, microwave irradiation (MW) 30 W, then EA (100 equiv.), MeOH/H_2O (1:1), 120 °C, 30 min, MW 30 W, then Ac_2O, pyridine, and DMAP **16iv**; 76%.

Scheme 2. Synthesis of di-, tetra-, and hexa-glucosamines.

the problem was soon traced to the increasing insolubility of the substrate as the deprotection of the TCP, CA, and acetyl groups progressed. Therefore, after partial deprotection had been carried out using EA in methanol, the reaction mixture was further treated with EA in a water/methanol mixture to complete the process. We also found that thermal reaction using microwave (MW) irradiation was effective, and that consecutive deprotection steps of **15iv-g** at 120 °C afforded **16iv**, which was isolated in 76% yield. Further applications of this protocol are now under active investigation.

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