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# A novel amino protecting group: DTPM

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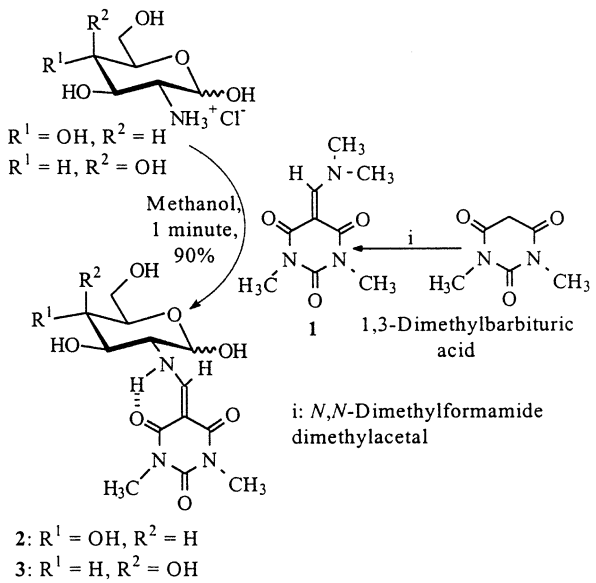
**Abstract**—A novel hydrazine and primary amine labile (1,3-dimethyl-2,4,6 (1*H*,3*H*,5*H*)-trioxopyrimidine-5-ylidene)methyl (DTPM) vinylogous amide type protecting group was developed to protect aminosugars and other primary amines in a facile and cost effective manner. 

Aminosugars are important constituents of various glycoconjugates[1] including peptidoglycans, mucopolysaccharides, glycopeptides and proteins and oligosaccharides of human milk and blood group determinants. Aminosugars are also often encountered in bacterial and tumor-associated carbohydrate antigens.[2] Oligosaccharide synthesis using 2-amino-2-deoxy sugars requires the presence of suitable amino protecting groups. For the preparation of 1,2-*trans*-glycosides, protecting groups such as phthaloyl,[3] tetrachlorophthaloyl,[4] trichloroethoxycarbonyl,[5] allyloxycarbonyl,[6] 2,5-dimethylpyrrole[7] or *N*,*N*-diacetyl[8] have been used. Recently, Schmidt and co-workers also proposed the use of thiodiglycoloyl[9] and dimethylmaleoyl[10] derivatives of D-glucosamine to synthesize 1,2-*trans*-linked glycosides. The azido group has received much attention in carbohydrate chemistry, since it serves as a masked, non-participating amino functionality, thereby allowing the synthesis of 1,2-*cis*-linked 2-amino-2-deoxy-glycosides.[11,12] Using the above mentioned protecting groups a large number of complex oligosaccharides containing aminosugars have been synthesized. However, these protecting groups always present some limitations. Difficulties of introduction or cleavage of a protecting group, stability or reactivity problems of the protected compounds can reduce overall yields. Development of novel protecting groups is important, providing new options in stability, orthogonality and reactivity.

Herein, we report the use of a non-acidic reagent suitable for vinylogous amide type protection of base sensitive primary amines in carbohydrate chemistry. DTPM protection can be achieved in high yield by reacting an amino sugar with the cheap 1,3-dimethyl-5-[(dimethylamino)methylene]2,4,6 (1*H*,3*H*,5*H*)-trioxopyrimidine[13] (DTPM-reagent) **1** in $H_2O$ or in organic solvents, such as methanol and $CH_2Cl_2$. The reaction usually goes to completion at room temperature with product precipitation in less than a minute when MeOH is used as solvent. The synthesis of (1,3-dimethyl-2,4,6 (1*H*,3*H*,5*H*)-trioxopyrimidine-5-ylidene)methyl (DTPM) protected aminosugars, the deprotection conditions and the stability of the protected carbohydrates towards a wide range of reaction conditions will be discussed.




**Scheme 1.**

*Keywords*: protecting groups; carbohydrates; vinylogous amides; primary amines.

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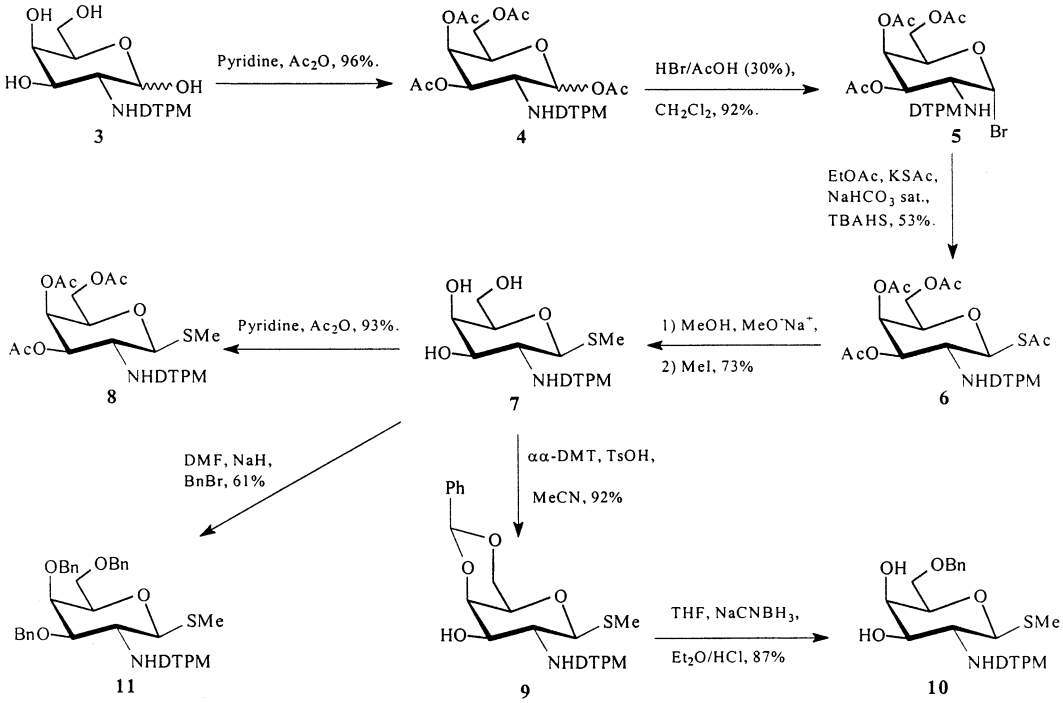


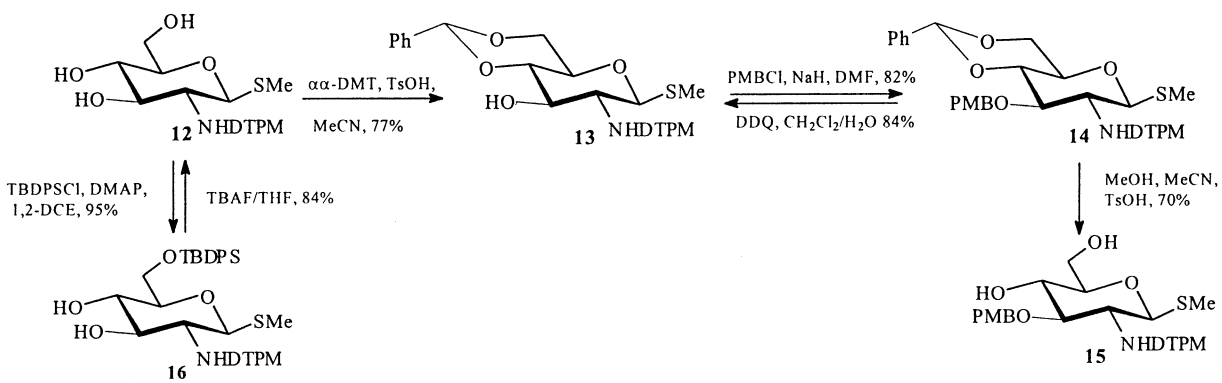

**Scheme 2.**

DTPM protected D-glucosamine **2** and D-galactosamine **3** were prepared in 90 and 86% yields, respectively, by reaction with **1** in MeOH (Scheme 1).[14]

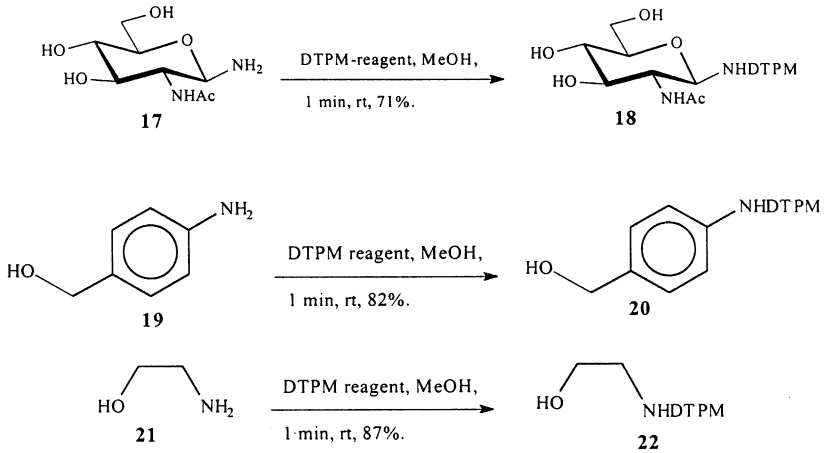
DTPM protected D-galactosamine **3** was acetylated with acetic anhydride in pyridine to afford peracetylated α/β-D-galactopyranose **4** in quantitative yield. Treatment of anomeric acetates **4** with HBr/AcOH (30%) in $CH_2Cl_2$ gave the glycosyl bromide **5**, which was reacted with potassium thioacetate in ethyl acetate, in the presence of a saturated solution of $NaHCO_3$ containing tetrabutylammonium hydrogensulfate, affording thioacetate **6** in 53% yield. Approximately 5% of the α-thioacetate was also formed in the reaction, thus multiple crystallizations were necessary to get the pure β-anomer **6**. Zemplen deprotection of peracetate **6** and subsequent treatment of the product with MeI gave thioglycoside **7** in 73% yield. Acetylation of β-thioglycoside **7** with acetic anhydride in pyridine gave peracetate **8**.

Benzylidene protection of DTPM protected thioglycoside **7** was carried out using α,α-dimethoxytoluene (α,α-DMT) in the presence of *p*-toluene sulphonic acid (TsOH) in MeCN affording the 4,6-*O*-acetal **9** in 92% yield. Reductive ring opening of DTPM protected acetal **9** using sodium cyanoborohydride in acidic conditions gave 6-*O*-benzyl thioglycoside **10** in 87% yield. Perbenzylation of thioglycoside **7** was achieved in DMF using NaH/benzyl bromide. Compound **11** was obtained in 61% yield (Scheme 2).

Treatment of methyl 2-deoxy-2-*N*-DTPM-amino-1-thio-β-D-glucopyranoside **12**[15] with α,α-dimethoxytoluene and TsOH in MeCN furnished 4,6-*O*-acetal **13** (77%), which was subsequently alkylated in DMF using *p*-methoxybenzyl chloride/NaH to give substituted benzyl ether **14** in 82% yield. Cleavage of the benzylidene moiety of **14** was carried out in MeOH/MeCN (1/10) in the presence of TsOH to provide diol **15** in 70% yield. Cleavage of the *p*-methoxybenzyl ether was realized in

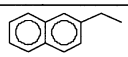
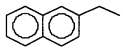



**Scheme 3.**




**Scheme 4.**

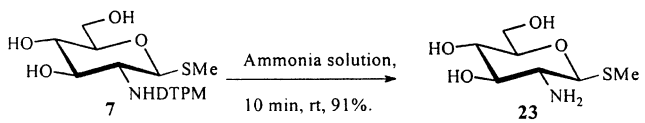
**Table 1.**

| Donors | R | Promotors | Solvent | Product | Yield (α/β) |
|---|---|---|---|---|---|
| **5** |  | AgOtf | 1,2-DCE | **24** | 72 (1/3) |
| **8** |  | DMTST | 1,2-DCE | **24** | 75 (2/3) |
| **8** | $-CH_2-CH_2-$ NHDTPM | DMTST | 1,2-DCE | **25** | 75 (2/3) |

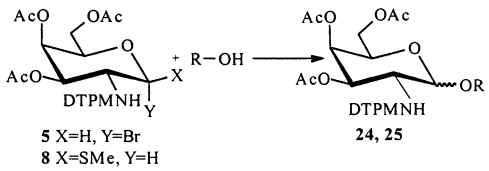
$CH_2Cl_2/H_2O$ (95/5) in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to afford compound **13** in 84% yield. Silylation of **12** using *tert*-butyldiphenylsilyl chloride (TBDPSCl)/dimethylaminopyridine (DMAP) in 1,2-dichloroethane (1,2-DCE) yielded 6-*O*-silyl **16** (95%). The *tert*-butyldiphenylsilyl protecting group was cleaved in 84% yield using tetrabutylammonium fluoride in THF (Scheme 3).

In addition to 2-deoxy-2-amino sugars, the DTPM group was shown to protect glycosylamine **17**[16] and the amino functions of 4-aminobenzyl alcohol **19** and ethanolamine **21** in high yields (Scheme 4).

Deprotection of the DTPM protecting group was easily achieved with ammonia, hydrazine or primary amines such as ethanolamine or hydroxylamine, at room temperature, in a few minutes (Scheme 5).[17]




**Scheme 5.**




**Scheme 6.**

In order to examine the influence of the DTPM protecting group on the stereochemical outcome of glycosylation reactions, experiments were performed using glycosyl donors **5** and **8** on a limited number of acceptors (DTPM protected ethanolamine and biphenolmethanol). The results (Scheme 6, Table 1) display predominantly the β product although a reasonable amount of the α glycoside was also formed (20–40%).

Stereochemical control of glycosylations using DTPM protected donors is currently under more detailed investigation.

In conclusion, the DTPM protecting group has demonstrated stability in most of the conditions commonly employed in carbohydrate chemistry including acylation, deacylation, alkylation, hydrogenolysis, acetal formation and cleavage, reductive ring opening of acetals, silylation and glycosylation. The advantageous features of this protecting group make it a viable alternative to existing methodologies in the synthesis of aminosugar containing carbohydrates.

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13. Synthesis of 1,3-dimethyl-5-[(dimethylamino)methylene]-2,4,6 (1*H*,3*H*,5*H*)-trioxopyrimidine **1**: *N*,*N*-dimethylformamide dimethyl acetal (252 g, 2.11 mol) was stirred at 0°C in $CHCl_3$ (750 mL). 1,3-Dimethylbarbituric acid (300 g, 1.92 mol) in $CHCl_3$ (2 L) was added to the stirring solution over 2 hours. The reaction mixture was washed with water (3×1 L) and saturated brine solution (1 L). The organic phase was dried over $MgSO_4$, filtered and evaporated to dryness under vacuum. The residue was re-suspended in diethyl ether (750 mL), filtered and washed on the funnel with additional diethyl ether (500 mL) to yield 1,3-dimethyl-5-[(dimethylamino)methylene]-2,4,6 (1*H*, 3*H*,5*H*)-trioxopyrimidine **1** as a yellow solid (271.85 g, 67%).
14. Sodium (2.66 g, 116 mmol) was dissolved in dry methanol (500 mL). The solution was left to return to room temperature. D-Galactosamine hydrochloride (25 g, 115.91 mmol) was added and the suspension was vigorously agitated for 8 minutes and filtered. DTPM reagent **1** (25.71 g, 1.05 equiv.) was dissolved in dry methanol (75 mL) and added to the aminosugar containing filtrate. The mixture was stirred at room temperature for 30 seconds. The product was filtered out and washed with diethyl ether (2×200 mL). Compound **3** was obtained in 85% yield as a white solid.
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17. DTPM protected D-glucosamine **7** (1 g) was taken up in ammonia solution (10 mL) and stirred at room temperature for 10 minutes. The resulting suspension was filtered and the filtrate washed with $CHCl_3$ (3×50 mL). The aqueous phase was evaporated to dryness to give compound **23** in 91% yield.