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N-Dimethylphosphoryl-protected glucosamine trichloroacetimidate as an effective glycosylation donor

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Abstract—Glycosylation of a variety of alcohols with 3,4,6-tri-*O*-acetyl-2-*N*-dimethylphosphoryl-2-deoxy-α-D-glucopyranosyl trichloroacetimidate as a glycosyl donor provided the corresponding coupled products in high yields and good β-selectivity. *N*-Dimethylphosphoryl-protection stayed stable under acidic and basic conditions for further elaboration of the glucosamine-containing oligosaccharides.

2-Amino-2-deoxy-D-glucopyranose (D-glucosamine) is an integral component of numerous biologically important prokaryotic and eukaryotic glycoconjugates.[1] Nevertheless, introduction of the glucosamine residue into oligosaccharides has been a long-standing problem in preparative carbohydrate chemistry.[2–19] It has been found that the 2-N-protecting groups always play a key role in glycosidic coupling with glucosamine derivatives as both donors[2–18] and acceptors.[19] A wide variety of the protecting groups for the 2-amino group of glucosamine have been developed, those include *N*-phthaloyl,[3] *N*-dichlorophthaloyl,[4] *N*-tetrachlorophthaloyl,[5] *N*-dithiasuccinoyl,[6] *N*-2,2,2-trichloroethoxycarbonyl,[7] *N*-trichloroacetyl,[8] *N*-trifluoroacetyl,[9] *N*,*N*-diacetyl,[10] *N*-acetyl-*N*-2,2,2-trichloroethoxycarbonyl,[11] *N*-*p*-nitrobenzyloxycarbonyl,[12] *N*-dimethylmaleoyl,[13] and *N*-dibenzyl group.[14] In addition, masking of the 2-amino group as 1,2-oxazoline,[15] azide,[16] dimethylpyrrole,[17] or the recent 2*N*,3*O*-oxazolidinone[18] also renders a choice for the synthesis of glucosamine-containing oligosaccharides. These protecting protocols have been proven successful to a certain extent; however, the non-generality of glycosylation and protection–deprotection conditions restricts their ubiquitous application.

Zervas and Konstas reported in 1960 the use of a 2-*N*-diphenylphosphoryl(DPP)-protected glucosamine 1-bromide (i.e., 3,4,6-tri-*O*-acetyl-2-*N*-DPP-2-deoxy-glucopyranosyl bromide) as a glycosyl donor.[20] Glycosylation with such a donor under Koenigs–Knorr conditions that employed poisonous heavy metal salts (e.g., $Hg(CN)_2$) as promoters gave the corresponding β-glycosides selectively albeit in very low yields. This has discouraged further application of these type of 2-*N*-phosphoryl-protected glucosamine derivatives in oligosaccharide synthesis.[21] However, one might envision the enhancement of the coupling efficiency by changing the leaving group to trichloroacetimidate, because glycosyl trichloroacetimidates have been proved to be, in general, superior to glycosyl bromides as glycosylation donors.[22] Thus, *N*-phosphoryl-protection shall find new applications in modern carbohydrate synthesis. Herein, we report the preliminary experimental results on this matter.[23]

Starting from D-glucosamine, 1,3,4,6-tetra-*O*-acetyl-β-D-glucosamine hydrochloride (**1**) was readily prepared in an overall 52% yield through three steps without the need of column chromatography, that is, condensation of the 2-amino group with *p*-anisaldehyde, acetylation of the remaining hydroxyl groups, and releasing of the 2-amino group with HCl in acetone (Scheme 1).[24] Treatment of amine **1** with diphenyl chlorophosphate in the presence of DMAP and Et_3N gave *N*-DPP-glucosamine derivative **2** in 96% yield. However, selective removal of

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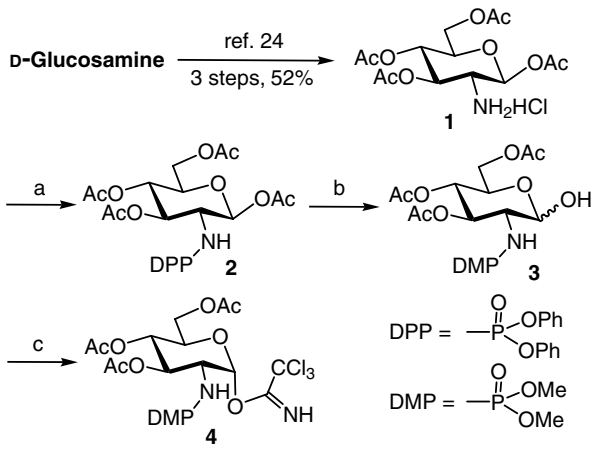
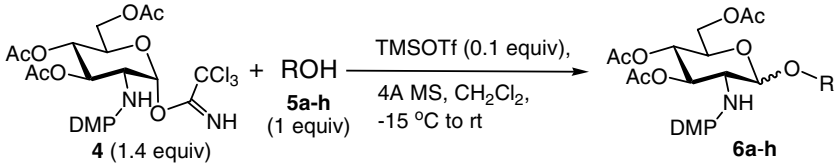


Scheme 1. Reagents and conditions: (a) $(PhO)_2POCl$ (2 equiv), DMAP (0.2 equiv), Et_3N (3 equiv), CH_2Cl_2, 0 °C to rt, 3 h, 96%; (b) NH_3, THF/MeOH (7:3), 0 °C, 40 min, 94%; (c) CCl_3CN (5 equiv), DBU (0.1 equiv), CH_2Cl_2, rt, 3 h, 82%.

the anomeric *O*-acetyl group on **2** met with difficulties; treatment with hydrazine acetate,[25] benzylamine,[26] or ethylene diamine[27] did not lead to clean reactions. Fortunately, upon subjection of compound **2** to ammonia in THF/MeOH, lactol product **3** was isolated in an excellent 94% yield, where the trans-esterification reaction also took place to convert the 2-*N*-DPP group into the 2-*N*-dimethylphosphoryl(DMP) group. Treatment of lactol **3** with CCl_3CN in the presence of DBU afforded α-trichloroacetimidate **4** in 82% yield, which was found stable under storage. The corresponding β-anomer was not detected.

To examine the donor properties of 2-*N*-DMP-protected glucosame imidate **4** in glycosylation, a series of alcohols (**5a**–**h**) were selected as acceptors, and a typical set of conditions for glycosylation with trichloroacetimidates (0.1 equiv of TMSOTf, 4 Å MS, CH_2Cl_2, rt, overnight)[22] was applied. The results are listed in Table 1. The corresponding coupling products (**6a**–**h**) were

Table 1. Glycosylation of alcohols (**5a**–**h**) with 3,4,6-tri-*O*-acetyl-2-*N*-DMP-2-deoxy-glucopyranosyl trichloroacetimidate (**4**)[a]



Entry	ROH	Product	β:α H-1 (ppm, *J*)	Yield (%)
1	AllOH (**5a**)	**6a**	β only 4.38, 8.1 Hz	88
2	*n*-$C_7H_{15}OH$ (**5b**)	**6b**	β only 4.32, 7.8 Hz	81
3	**5c**	**6c**	β only 4.40, 7.9 Hz	92
4[b]	**5d**	**6d**	4.3:1 4.82, 8.4 Hz (β) 5.40, br s (α)	95
5[b]	**5e**	**6e**	3.2:1, 4.94, 7.8 Hz (β) 5.50, 3.0 Hz (α)	89
6	**5f**	**6f**	β only 4.49, 7.8 Hz	85