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Metal-catalyzed Stereoselective and Protecting-group-free Synthesis of 1,2-*cis*-Glycosides Using 4,6-Dimethoxy-1,3,5-triazin-2-yl Glycosides as Glycosyl Donors

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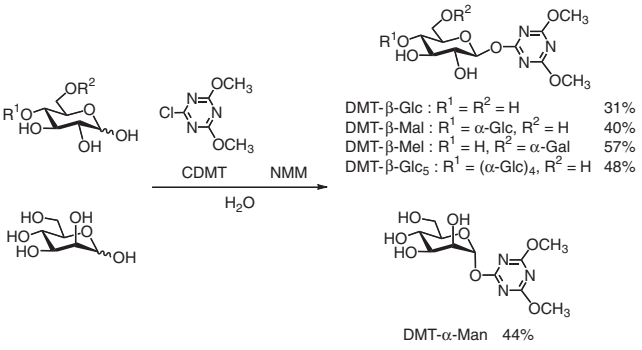
4,6-Dimethoxy-1,3,5-triazin-2-yl glycosides, glycosyl donors prepared in one step from free saccharides without protection of the hydroxy groups, were stereoselectively and equivalently converted to the corresponding 1,2-*cis*-glycosides by using a catalytic amount of metal catalyst. This reaction was successfully applied not only to monosaccharides, but also to di- and oligosaccharides.

The development of chemical glycosylation reactions for the efficient production of carbohydrates and for specific biological applications has been an important pursuit in chemical research since the first report on glycosylation by Fischer in 1893.[1] Fischer glycosylation is the simplest and most direct route for the synthesis of unprotected alkyl glycosides in the presence of an acidic catalyst at high temperatures in an alcohol solvent, and remains one of the most popular methods owing to its simplicity and versatility.[2] A critical issue in chemical glycosylation is stereoselectivity at the anomeric position.[3] It is well known that anomeric effect,[4] neighboring group participation,[5] solvent effect of nitrile solvents,[6] and through-space effect[7] are efficient approaches for stereoselective glycosylation, and several glycosyl donors, e.g., thioglycoside,[8] glycosyl iodide,[9] and glycosyl trichloroimidate,[10] stereoselectively provide glycosyl products in conjunction with activators under appropriate reaction conditions. However, the synthesis of these glycosyl donors from free saccharides requires multistep processes, including protection of all the hydroxy groups, activation or selective deprotection at the anomeric position, and the introduction of leaving groups.

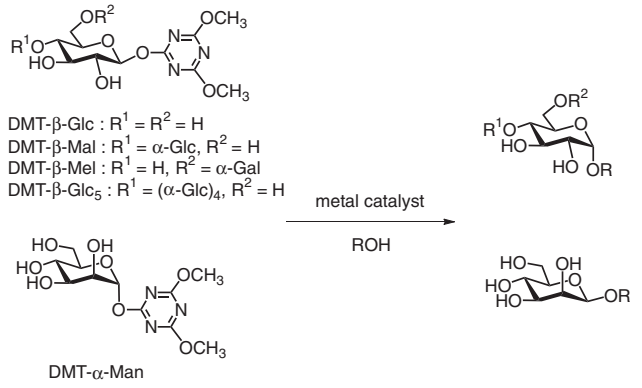
We recently reported that free saccharides can be directly converted to the corresponding 4,6-dimethoxy-1,3,5-triazin-2-yl (DMT)-glycosides in water without protecting the hydroxy groups, using a dehydrative condensing agent, 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-morpholinium chloride (DMT-MM).[11] The resulting DMT-glycosides were recognized by the corresponding glycosidases and acted as efficient glycosyl donors for enzymatic glycosylation catalyzed by glycosidases, e.g., endo-β-1,4-glucanase, α-*N*-acetylglucosaminidase, α-*N*-acetylgalactosaminidase, α-L-arabinofuranosidase, and *exo*-chitosanase.[12] However, little has been reported regarding chemical glycosylation using 1,3,5-triazin-2-yl glycosides as glycosyl donors.[13] Fujimoto et al. reported a chemical glycosylation using a protected DMT-glycoside and a molar equivalent of Lewis acid, but the reaction was not stereoselective. Schmidt et al. also reported chemical glycosylations using several 1,3,5-triazin-2-yl glycosides, for example, 4,6-dichloro-, 4-chloro-6-methoxy-, and 4-chloro-6-diisopropylamino-1,3,5-triazin-2-yl glycosides. In this letter, we report a metal-catalyzed stereoselective glycosylation reaction using DMT-glycosides prepared in one step and then used as glycosyl donors. This reaction is applicable not only to monosaccharides, but also to di- and oligosaccharides.

A typical procedure for preparing DMT-glycoside involves stirring an aqueous solution of the free saccharide, 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT), and *N*-methylmorpholine (NMM) for 24 h at room temperature (Scheme 1). The resulting products were purified by silica gel column chromatography. The nucleophilic substitution reaction between the anomeric hydroxy group of the free saccharide and CDMT occurred smoothly in the presence of a base in aqueous media since the acidity of the hemiacetal anomeric hydroxy group is much higher than that of other hydroxy groups and water;[14] the reaction afforded the corresponding DMT-glycoside. D-Glucose (Glc), maltose (Mal), melibiose (Mel), and maltopentaose (Glc_5), which have an equatorial hydroxy group at the 2-position, provided DMT-β-glycosides, whereas DMT-α-glycoside was obtained from D-mannose (Man), which has an axial hydroxy group at the 2-position.[15]

The synthesis of alkyl glycosides using DMT-glycosides as glycosyl donors was conducted in various anhydrous alcohol

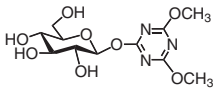
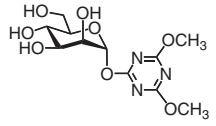
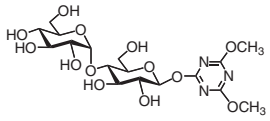
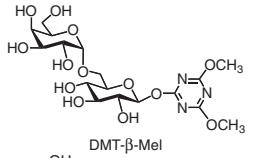
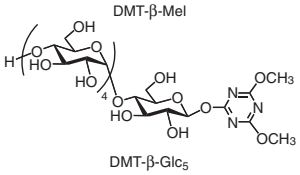


Scheme 1. Synthesis of DMT-glycosides from free saccharides.



Scheme 2. Metal-catalyzed synthesis of alkyl glycosides using DMT-glycosides.

Table 1. Synthesis of alkyl glycosides using DMT-glycosides

Entry	Substrate	ROH[a]	Catalyst[b]	Time /h	Temp. /°C	Yield[c] /%	α/β[c]
1	 DMT-β-Glc	MeOH	$[Cu^{I}(CH_3CN)_4]PF_6$	2	r.t.	quant.	α only
2		MeOH	$[Ag^{I}(CH_3CN)_4]BF_4$	1	r.t.	quant.	α only
3		MeOH	$[Pd^{II}(CH_3CN)_4](BF_4)_2$	1	r.t.	quant.	α only
4		MeOH	bis(2,4-pentanedionato)Pd(II)	72	r.t.	quant.	α only
5		MeOH	bis(2,4-pentanedionato)Cu(II)	120	r.t.	35	α only
6		EtOH	$[Cu^{I}(CH_3CN)_4]PF_6$	3	r.t.	quant.	96/4
7		*i*-PrOH	$[Cu^{I}(CH_3CN)_4]PF_6$	4	r.t.	quant.	95/5
8		*tert*-BuOH	$[Cu^{I}(CH_3CN)_4]PF_6$	5	30	quant.	96/4
9	 DMT-α-Man	MeOH	$[Cu^{I}(CH_3CN)_4]PF_6$	3	r.t.	90	30/70
10		EtOH	$[Cu^{I}(CH_3CN)_4]PF_6$	4	r.t.	90	30/70
11		*i*-PrOH	$[Cu^{I}(CH_3CN)_4]PF_6$	5	r.t.	87	30/70
12		MeOH	$[Ag^{I}(CH_3CN)_4]BF_4$	1	r.t.	84	27/73
13		MeOH	$[Pd^{II}(CH_3CN)_4](BF_4)_2$	1	r.t.	87	32/68
14		MeOH/MeCN[d]	$[Cu^{I}(CH_3CN)_4]PF_6$	22	r.t.	86	30/70
15	 DMT-β-Mal	MeOH	$[Cu^{I}(CH_3CN)_4]PF_6$	5	r.t.	quant.	α only
16		EtOH	$[Cu^{I}(CH_3CN)_4]PF_6$	5	r.t.	quant.	94/6
17	 DMT-β-Mel	MeOH	$[Cu^{I}(CH_3CN)_4]PF_6$	2	r.t.	quant.	α only
18		EtOH	$[Cu^{I}(CH_3CN)_4]PF_6$	2	r.t.	quant.	97/3
19	 DMT-β-Glc$_5$	MeOH	$[Cu^{I}(CH_3CN)_4]PF_6$	24	r.t.	quant.	α only

[a]All reactions were conducted in a large excess of alcohol. [b]0.1 equiv. [c]Determined by ^{1}H NMR measurements of the reaction mixture. [d]Solvent was MeOH/MeCN = 1/1 (v/v).

solvents in the presence of a catalytic amount of metal catalyst (Scheme 2 and Table 1). An excess of alcohol was added to a mixture of DMT-glycoside and 0.1 equiv of metal catalyst under nitrogen atmosphere and stirred at room temperature. The metal catalyst was removed by using a metal scavenger at the completion of the reaction; after filtering, the filtrate was evaporated in vacuo and subjected to NMR analysis to determine the yield and α/β ratio. The treatment of 4,6-dimethoxy-1,3,5-triazin-2-yl β-D-glucopyranoside (DMT-β-Glc) with methanol in the presence of tetrakis(acetonitrile)copper(I) hexafluorophosphate ($[Cu^{I}(CH_3CN)_4]PF_6$), tetrakis(acetonitrile)silver(I) tetrafluoroborate ($[Ag^{I}(CH_3CN)_4]BF_4$), or tetrakis(acetonitrile)palladium(II) tetrafluoroborate

($[Pd^{II}(CH_3CN)_4](BF_4)_2$) for 1–2 h yielded α-methyl glucopyranoside stereoselectively and quantitatively (Entries 1–3). The product was isolated by silica gel column chromatography and analyzed by NMR spectroscopy. The anomeric proton signal is a doublet with $J_{1,2} = 3.6$ Hz, indicating an α-glucoside. The use of bis(2,4-pentanedionato)palladium(II) or bis(2,4-pentanedionato)copper(II) as catalyst required longer reaction times to obtain the product (Entries 4 and 5). The α-alkyl glucosides ethyl, *i*-propyl, and *tert*-butyl were obtained stereoselectively following reaction for several hours, catalyzed by with $[Cu^{I}(CH_3CN)_4]PF_6$ in primary, secondary, and tertiary alcohols (Entries 6–8). This stereoselective synthesis of alkyl glycosides catalyzed by Cu(I) using DMT-glycosides as glycosyl donors was applicable not only to monosaccharides, but also to the di- and oligosaccharides Mal, Mel, and Glc_5 (Entries 15–19). Application of the classic Fischer method to Mel, a disaccharide with an acid-labile α-1,6 bond, resulted in complete destruction of the glycosidic bond by the acid catalyst.[16] In contrast, the present method using a metal catalyst under neutral conditions allowed even an acid-labile oligosaccharide to be glycosylated without cleavage of the inner glycosidic bond and clearly indicated that the anomeric position of the oligosaccharide could be activated in a regiospecific manner.

We next attempted the synthesis of β-mannoside using 4,6-dimethoxy-1,3,5-triazin-2-yl α-D-mannopyranoside (DMT-α-Man). Use of $[Cu^{I}(CH_3CN)_4]PF_6$ as a catalyst in methanol provided the β-enriched product (α/β ratio = 30/70) and the $J_{C,H}$ coupling constant of the anomeric carbon in the main product was 160.0 Hz as determined by ^{13}C NMR spectroscopy (Entry 9 and Figure S12). It is well known that the $J_{C,H}$ couplings of β- and α-mannopyranosyl anomeric carbons are around 160 and 170 Hz, respectively.[17] NOESY NMR analysis also indicated that the main product was β-mannoside, as the anomeric proton showed cross-peaks with the 2-, 3-, and 5-position protons. The $J_{C,H}$ of the anomeric carbon in the minor product was 169.0 Hz, indicating α-configuration (Figure S14). The use of other alcohols (ethanol and *i*-propanol) and other metal catalysts (Ag(I) and Pd(II)) also provided product α/β ratios of approximately 30/70 (Entries 10–14). The addition of acetonitrile slowed the reaction but did not affect the α/β ratio of the product. The use of Lewis acids, such as trimethylsilyl trifluoromethanesulfonate (TMSOTf), AgCl, and $ZnCl_2$, also provided β-enriched product but did not affect the α/β ratio of the product (data not shown).

Although the detailed reaction mechanism remains unclear, the preferential formation of 1,2-*cis*-glycoside suggests that the reaction proceeds via a stereospecific S_N2-type mechanism. It is assumed that the nitrogen atom in the triazine ring or the glycosidic oxygen is protonated by the metal, and the anomeric center is activated. DMT-β-glycosides were almost completely converted to α-glycosides. In contrast, DMT-α-Man provided β-enriched mannoside, suggesting that an S_N2-type reaction preferentially occurred at the anomeric position of DMT-α-Man; the mixture of β- and α-mannosides indicated that an S_N1-type reaction occurred nonpreferentially via an oxocarbenium ion intermediate.

In conclusion, the stereoselective synthesis of alkyl glycosides using DMT-glycosides as glycosyl donors, directly prepared from free saccharides in water, was achieved by using a catalytic amount of metal catalyst and provided 1,2-*cis*-glycosides, such as α-glucoside and β-mannoside, by using 1,2-*trans*-glycosides, e.g., DMT-β-Glc and DMT-α-Man. It is noteworthy that the present method is applicable not only to monosaccharides, but also to di- and oligosaccharides and may provide a new approach for glycosylation reactions in synthetic carbohydrate chemistry.

Supporting Information is available electronically on J-STAGE.

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15 In this reaction, disubstituted by-products having DMT groups at 1 and 2 positions of saccharide moiety were formed; 4,6-dimethoxy-1,3,5-triazin-2-yl-2-*O*-(4,6-dimethoxy-1,3,5-triazin)-α-D-glucopyranoside and 4,6-dimethoxy-1,3,5-triazin-2-yl-2-*O*-(4,6-dimethoxy-1,3,5-triazin)-β-D-mannopyranoside etc., which were removed by column chromatography.
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