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High -Yielding Catalytic Synthesis of Glycosyl Azides from Peracylated Sugars

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In the presence of a catalyst generated from $SnCl_4$ and $AgClO_4$, or $Yb(OTf)_3$, various glycosyl azides are synthesized in high yields with complete stereoselectivities from peracylated sugars and trimethylsilyl azide by choosing a suitable solvent such as dichloromethane or nitromethane.

Glycosyl azides are important derivatives in carbohydrate chemistry and are used as synthetic precursors of fragments of *N*-glycoprotein glycans1) or as chiral auxiliaries2) in the syntheses of amino acids,2a, 2b) α-amino phosphonic acids,2c) homoallylamines,2d) β-amino carbonyl compounds,2e, 2f) and amino nitrile derivatives.2g) Therefore, highly efficient and stereoselective synthesis of various glycosyl azides from simple sugar derivatives is considered to be a very important problem.

General methods for the synthesis of glycosyl azides are classified into the following three classes: 1) preparation from glycosyl halides and metal azides such as LiN_3, NaN_3, or AgN_3,3) 2) preparation from 1-O-acyl sugars and trimethylsilyl azide using a Lewis acid catalyst (BF_3-OEt_2 or $SnCl_4$),4) 3) phase transfer reactions.1e,1g, 5) Recently, Fuchs *et al.* have reported a convenient and high-yielding synthesis of glycosyl azides from glycosyl halides and 1,1,3,3-tetramethylguanidinium azide except in the case of mannosyl azide.6) However, the above mentioned methods have some disadvantageous problems such as instability of the glycosyl donors (prepared from 1-O-acyl sugars), requisition for heating in high boiling solvent, and requisition for a full equivalent of phase transfer reagent using large excess amount of NaN_3.

The glycosylation reaction of penta-O-pivaloyl-β-D-galactopyranose with trimethylsilyl azide catalyzed by $SnCl_4$ affords the corresponding glycosyl azide in high yield (93%),4c) however, the reported yields for other substrates such as 1b, 3b and 6b were only moderate.3d, 4) In this communication, we would like to describe an efficient method for the synthesis of various glycosyl azides starting from peracylated sugars and trimethylsilyl azide using a Lewis acid catalyst.

In the first place, several Lewis acid catalysts were screened by taking a reaction of 1,2,3,4,6-penta-O-acetyl-β-D-glucopyranose (**1a**) with trimethylsilyl azide (see Table 1). Consequently, the best result was obtained when the catalyst7) generated in situ from $SnCl_4$ and $AgClO_4$ was employed. In the above glycosylation of various glycosyl donors with trimethylsilyl azide using the Sn(IV) catalyst having perchlorate anion, a catalytic cycle is more efficiently made up to afford the desired glycosyl azides in nearly quantitative yields (see Table 2). Concerning the effect of solvents, the desired glycosyl azide was obtained in good yield when dichloromethane was used.

Next, the use of $Yb(OTf)_3$ catalyst was tried. As indicated in Table 1, no reaction took place in

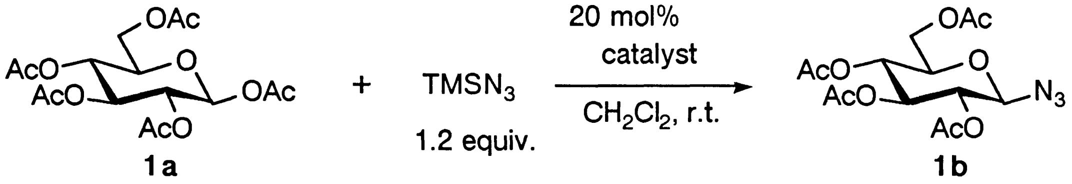


Table 1. Effect of catalysts

Entry	Catalyst	Time / h	Yield / %
1	$SnCl_4$ - $AgClO_4$	6	96
2	$SiCl_4$ - $AgClO_4$	10	65
3	$MeSiCl_3$ - $AgClO_4$	10	79
4	$SnCl_2$ - $2AgClO_4$	10	85
5	$Sn(OTf)_2$	10	N.R.
6	$Yb(OTf)_3$	10	N.R.

dichloromethane under the same reaction conditions as the above. On the other hand, it was observed that the reaction proceeded smoothly in nitromethane to give the desired glycosyl azide, though slightly lower yield in comparison with the preceding reaction using the Sn(IV) catalyst. Furthermore, it was also found that the same result (yield = 85%) was obtained in the glycosylation of **1a** with trimethylsilyl azide by the reused $Yb(OTf)_3$, which was recovered from aqueous phase and dried at 200 °C *in vacuo* for 22 h prior to use.[8] Several examples for the synthesis of glycosyl azides are demonstrated in Table 3. In the cases when the other glycosyl donors were employed, the corresponding glycosyl azides were also obtained in excellent yields. Thus, the glycosylation catalyzed by $Yb(OTf)_3$ was dramatically promoted in nitromethane solvent. Concerning $Yb(OTf)_3$ catalyst in the glycosylation, Inanaga *et al.* have recently employed $Yb(OTf)_3$ in the glycosylation reaction of so-called armed sugars such as 1-O-methoxyacetyl-2,3,4,6-tetra-O-benzyl-D-glucopyranose or 1-O-methoxyacetyl-2,3,5-tri-O-benzyl-D-ribofuranose with various alcohols in several solvents such as acetonitrile or dichloromethane. It was shown there that the 1-O-acetyl analogues of the sugars were not activated by $Yb(OTf)_3$ under similar conditions and methoxyacetyl leaving group, a bidentate ligand, was essential for the activation.[9]

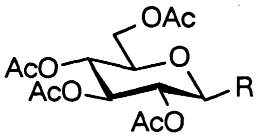
A typical experimental procedure for the preparation of 1,3,4,6-tetra-O-acetyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-β-D-glucopyranosyl azide (**5b**) from **5a** and trimethylsilyl azide using a catalyst generated from $SnCl_4$ and $AgClO_4$ is as follows; a solution of $SnCl_4$ (0.01 mmol) in toluene (0.1 ml) was added to a stirred suspension of $AgClO_4$ (0.01 mmol) in dichloromethane (2 ml) at room temperature, and the mixture was shielded from a light and stirred for 1 h. To this mixture was added a solution of **5a** (0.2 mmol) and trimethylsilyl azide (0.24 mmol) in dichloromethane (2 ml) at room temperature. After stirring the mixture for 5 h, aqueous sodium hydrogen carbonate was added. Usual work up and separation by column chromatography on silica gel afforded the desired glycosyl azide in quantitative yield.

Thus, high-yielding catalytic synthesis of various glycosyl azides was successfully carried out just starting from 1-O-acetyl sugars and trimethylsilyl azide using a catalyst generated from $SnCl_4$ and $AgClO_4$ without

$$\textbf{1a - 7a} \quad + \quad \underset{\text{1.2 equiv.}}{\text{TMSN}_3} \quad \xrightarrow[\text{CH}_2\text{Cl}_2\text{, r.t.}]{\text{SnCl}_4\text{ - AgClO}_4} \quad \textbf{1b - 7b}$$

Table 2. Synthesis of glycosyl azides using Sn(IV) catalyst

Entry	Donor	Catalyst / mol%	Time / h	Isolated yield / %
1	**1a**	20	8	99
2	**2a**	20	8	98
3	**3a**	10	3	quant.
4	**4a**	20	5	98
5	**5a**	5	5	quant.
6	**6a**	10	7	98
7	**7a**	5	5	quant.



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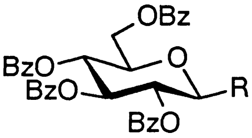

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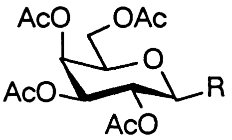

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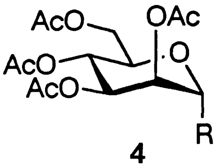

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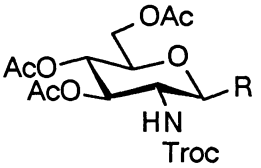

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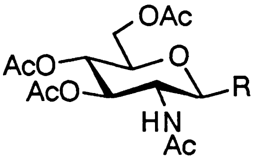

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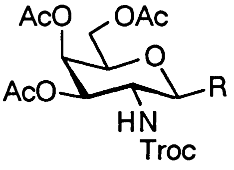

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1a - 7a : R = OAc
1b - 7b : R = N_3

$$\textbf{1a, 3a, 5a, 7a} \quad + \quad \underset{\text{1.2 equiv.}}{\text{TMSN}_3} \quad \xrightarrow[\text{MeNO}_2\text{, r.t.}]{\text{Yb(OTf)}_3} \quad \textbf{1b, 3b, 5b, 7b}$$

Table 3. Synthesis of glycosyl azides using $Yb(OTf)_3$

Entry	Donor	Catalyst / mol%	Time / h	Isolated yield / %
1	**1a**	20	8	85
2	**3a**	20	6	94
3	**5a**	10	3	97
4	**7a**	10	3	97

necessity of converting the sugars into glycosyl halides. In addition, $Yb(OTf)_3$ was also employed as an effective catalyst by choosing a suitable solvent, and repeatedly reused after recovering from aqueous phase.

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