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# A Simple and Convenient Synthesis of Glycosyl Azides

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### A SIMPLE AND CONVENIENT SYNTHESIS OF GLYCOSYL AZIDES

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ABSTRACT: Treatment of glycosyl halides with NaN<sub>3</sub> in aqueous acetone or acetonitrile is a convenient method for the stereoselective synthesis of 1,2-transper-O-acetyl-glycosyl azides.

Glycosyl azides as synthetic precursors of glycosyl amines and consequently glycopeptides are important class of carbohydrate derivatives.

There are several procedures for the preparation of 1,2-*trans*-per-O-acetylglycosyl azides<sup>1, 2</sup>. The classical method involves treatment of glycosyl halides with metal azides at heating in DMF and affords moderate yields<sup>3</sup>.

A method utilizing phase transfer reaction conditions is more efficient but requires one equivalent of phase transfer reagent and up to 5 equivalents of sodium azide<sup>4</sup>.

Recently, 1,1,3,3-Tetramethylguanidinium azide has been suggested as an excellent reagent for a conversion of glycosyl halides to glycosyl azides<sup>5</sup>. The method affords almost quantitative yields under very mild conditions, but has one

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disadvantage, related with an absence of a commercially available 1,1,3,3tetramethylguanidinium and a necessity of a special preparation of the reagent.

We describe herein a simple and effective synthesis of 1,2-*trans*-per-O-acetylglycosyl azides by reaction of glycosyl halides with sodium azide in aqueous acetone as a solvent.



Entry	Substrate	Yield (%)
1	$R_1 = R_2 = H, R_3 = R_4 = OAc, X = Br$	73
2	$R_1$ =CH <sub>2</sub> OAc, $R_2$ =H, $R_3$ =R <sub>4</sub> =OAc, X=Br	79
3	$R_1$ =CH <sub>2</sub> OAc, $R_2$ =R <sub>4</sub> =OAc, $R_3$ =H, X=Br	72
4	$R_1$ =CH <sub>2</sub> OAc, $R_2$ =H, $R_3$ =OAc, $R_4$ =NHAc, X=Cl	70
5	$R_1 = CH_2OAc$ , $R_2 = H$ , $R_3 = \beta - D - Glc(OAc)_4$ , $R_4 = OAc$ , $X = Br$	76
6	$R_1$ =CH <sub>2</sub> OAc, $R_2$ =H, $R_3$ = $\alpha$ -D-Glc(OAc) <sub>4</sub> , $R_4$ =OAc, X=Br	67

It is known that although glycosyl halides are sensitive to hydrolysis, they have been employed successfully for preparation of aryl and alkyl 1-thioglycosides by reaction with phenolate and thiolate anions in acetone-water mixture<sup>6, 7.</sup> The high yields of the reactions show that the hydrolysis is not essential.

We have found that the same reaction conditions can be used for a glycosyl azide synthesis. So, treatment of glycosyl halides in aqueous acetone or acetonitrile with sodium azide for 2-2.5 hours at room temperature affords glycosyl azides with good yields. The reaction is stereoselective with complete inversion at the anomeric center. A presence of water in the reaction mixture is very important. Without it the reaction does not proceed. So, we found only traces of glycosyl

azide after reflux for several hours of 2,3,4,6-tetra-O-acetyl- $\alpha$ -D-glucopyranosyl bromide and sodium azide in dry acetonitrile. Most of the glycosyl halide was unchanged. After an addition of water to the reaction mixture the conversion was over in 2 hours at room temperature.

The reason why water accelerates the reaction mainly consists in a low activity of azide ion in anhydrous solvents, including DMF, caused by poor solubility of NaN<sub>3</sub>. Dissolving NaN<sub>3</sub>, water increases a concentration of azide ion and thus the reaction rate. As a confirmation of this we found that in the presence a full equivalent of Dibenzo-18-Crown-6, glycosyl halides readily react with NaN<sub>3</sub> in a dry acetonitrile at room temperature, with almost the same reaction rate. Interestingly, an addition of aqueous solution of NaN<sub>3</sub> to a stirred solution of acetobromoglucose in DMF at room temperature caused full hydrolysis of the halogenose in a few minutes.

The title compounds, prepared using suggested procedure with good yields as crystalline solids, were homogeneous by TLC and <sup>1</sup>H NMR spectroscopy. The physical data of all known compounds were in full agreement with literature values. All compounds were characterized by elementary analysis and NMR spectroscopy.

In conclusion, a practical alternative procedure has been developed for the conversion of glycosyl halides into glycosyl azides. It has been shown that the combination of water-acetone (or acetonitrile) as the reaction solvent is more efficient for the conversion than dry DMF. High boiling solvents and heating is not required. Only inexpensive, readily available reagents were used.

GENERAL PROCEDURE: To glycosyl halide (5.0 mmol) in acetone (18 ml) was added solution of NaN<sub>3</sub> (0.39 g; 6.0 mmol) in H<sub>2</sub>O (4.5 ml). The reaction mixture was stirred at room temperature until TLC indicated total disappearance of the halide. Solvent was evaporated at reduced pressure. The products usually crystallized spontaneously during the concentration. The solid was suspended in water, filtered and washed with water. Recrystallization from ethanol afforded pure glycosyl azides.

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