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C-Glycosyl 1,2,4-triazoles: Synthesis of the 3-β-D-glucopyranosyl-1,5-disubstituted and 5-β-D-glucopyranosyl-1,3-disubstituted variants

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ABSTRACT

Highly variable synthetic routes were elaborated toward trisubstituted *C*-glycopyranosyl 1,2,4-triazoles. *N*-Acyl-thioamide derivatives were obtained by acylation of *O*-perbenzoylated 2,6-anhydro-D-*glycero*-D-*gulo*-heptonothioamide by acid chlorides and of thioamides by *O*-perbenzoylated 2,6-anhydro-D-*glycero*-D-*gulo*-heptonoyl chloride. These precursors reacted with substituted hydrazines in a regioselective manner to yield 3-β-D-glucopyranosyl-1,5-disubstituted- and 5-β-D-glucopyranosyl-1,3-disubstituted-1,2,4-triazoles, respectively. Analogous *N*-acyl-2,6-anhydro-heptonamides failed to give the above triazoles with hydrazines. *O*-Deprotection of the *C*-glucosyl 1,2,4-triazoles by the Zemplén method furnished test compounds which showed no inhibition against rabbit muscle glycogen phosphorylase *b*.

1. Introduction

Although 1,2,4-triazoles have not been found as constituents of natural compounds, this heterocycle is frequently part of biologically active synthetic molecules, among them a wide range of marketed drugs and agricultural chemicals, and finds various applications in many other fields, e.g. in synthetic and analytical chemistry, uses as corrosion inhibitors, ligands of metal complexes, and functional materials. As a consequence of this broad utility and interest, a large variety of synthetic methods have been elaborated to get this heteroring and its derivatives resulting in miriads of 1,2,4-triazole containing compounds.[1–8]

Carbohydrate derivatives of this heterocycle are much less available. Direct conjugation of the 1,2,4-triazole ring with sugars may occur by a C–N or a C–C bond. From the former class several examples of bioactive nucleoside analogues[9] and N^1-[10–13] as well as N^4-glycopyranosides[14] have been known. *C*-Glycosyl 1,2,4-triazoles are an even more uncommon type[15–18] and only in recent years has progress been made in this field with the syntheses of 3-glycopyranosyl-5-substituted-1,2,4-triazoles as glycogen phosphorylase inhibitors for potential antidiabetic use.[19–24]

As a continuation of our efforts in the above syntheses, the preparation of trisubstituted *C*-glycopyranosyl 1,2,4-triazoles was envisaged to generate molecules for structure–activity relationships of glycogen phosphorylase inhibitors and also for other potential biological applications. From the three possible isomeric structures (Scheme 1) some examples of the 3-glycosyl-4,5-disubstituted-1,2,4-triazoles (**I**) were already described,[21] therefore, this work has focused on the 3-β-D-glucopyranosyl-1,5-disubstituted (**II**) and 5-β-D-glucopyranosyl-1,3-disubstituted (**III**) counterparts.

2. Results and discussion

A retrosynthetic analysis of the target compounds (Scheme 1) revealed two types of synthetic possibilities. Type **A** syntheses would require a 1,3-dipolar cycloaddition of nitriles with nitrilimines. Toward triazoles **II** route **A** would require a series of nitriles **IV** which themselves may also have to be prepared from other kinds of starting materials and *C*-glycosyl nitrilimine precursors with appropriate substituents like 5-glycosyl-2-substituted-tetrazoles **V** or hydrazonoyl halide derivatives of anhydro-aldonic acids **VI** which are also not readily available. Toward triazoles **III** route **A** would need well known glycosyl cyanides **X** and nitrilimine precursors such as 2,5-disubstituted-tetrazoles **XI** or hydrazonoyl halides **XII**. Actually, the latter type reaction (**X** + **XII**) was studied to some extent, and a few 3-β-D-glycopyranosyl-1,5-disubstituted-1,2,4-triazoles were described.[16,17] However, for getting a large series of compounds, multistep synthesis of each hydrazonoyl halide and/or 2,5-disubstituted-tetrazole would be necessary. These

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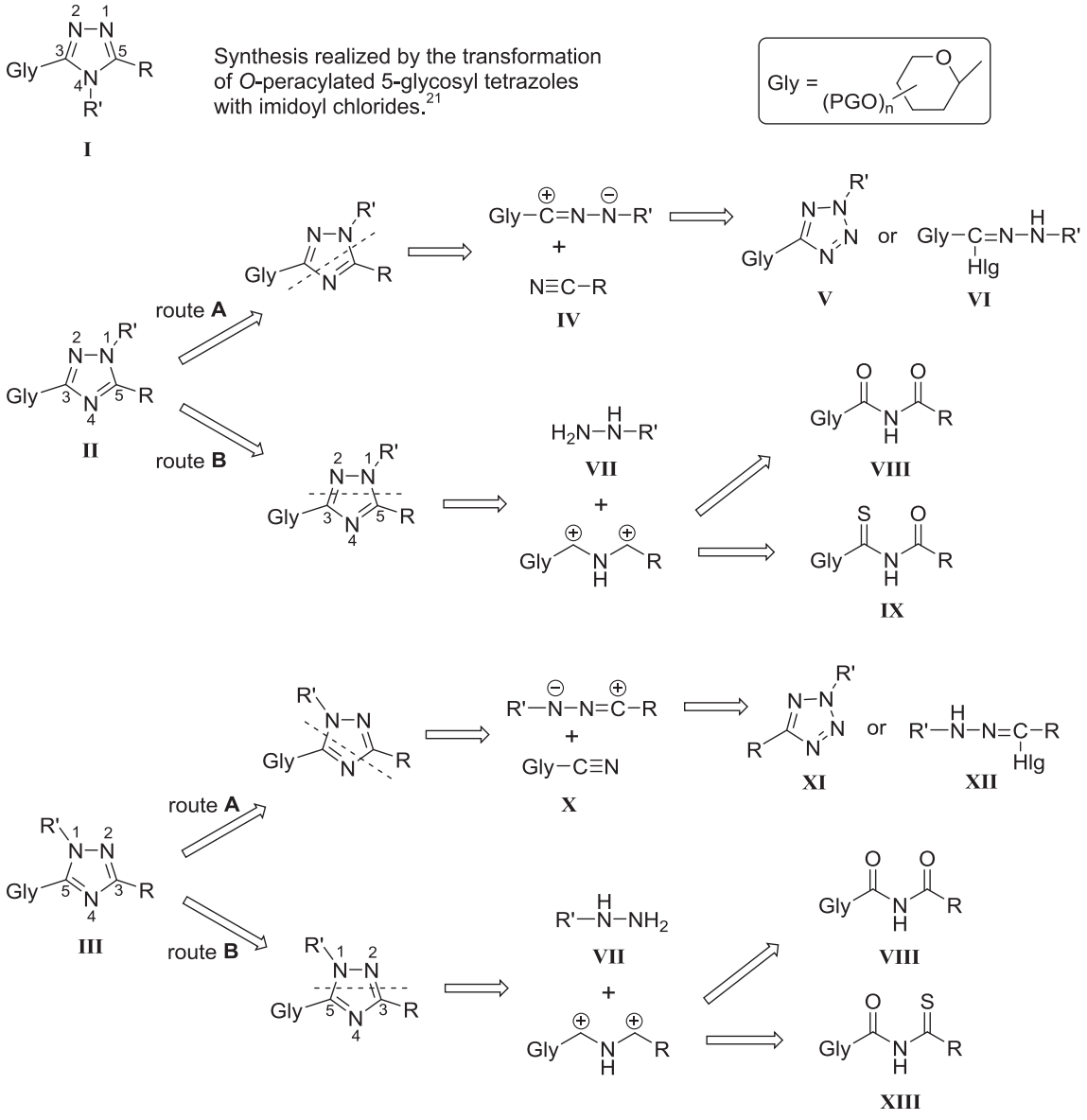
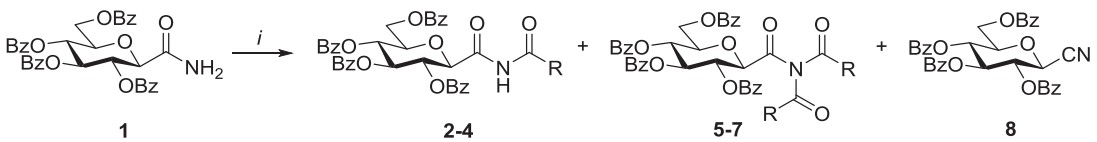


Scheme 1. Isomers of trisubstituted *C*-glycopyranosyl 1,2,4-triazoles (**I-III**) and retrosynthetic analysis of the target compounds **II** and **III**.

requirements adumbrate rather labour intensive preparative work to get the precursors for both route **A** type syntheses. Therefore we turned to type **B** synthetic pathways which would need various hydrazines **VII** and acylation of easily available *C*-glycosyl formamides (anhydro-aldonamides) to get precursors **VIII**. In these cases the regioselectivity may be a challenge due to the possibly similar reactivity of the two electrophilic centres of **VIII**, therefore, the related acyl-thioamides **IX** and **XIII** were also taken into

Table 1
Experiments towards acylation of 2,6-anhydro-heptonamide **1**.



i) 5 equiv. RCOCl, 5 equiv. pyridine, dry $CHCl_3$, rt

R	Yield (%)		
Me	**2** (51)	**5** (34)	–
Ph	**3** (26)	**6** (8)	**8** (67)
1-Naphthyl	**4** (16)	**7** (15)	**8** (39)