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Synthesis of 1,2,3-triazolylpyranosides through click chemistry reaction

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ABSTRACT

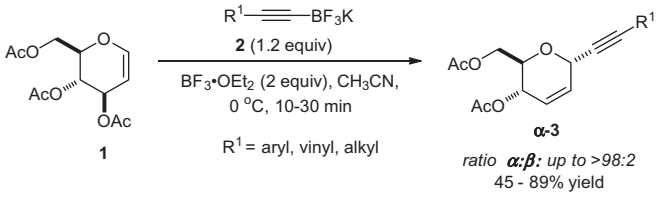
We have developed an efficient method for the synthesis of functionalized *C*-glycosyl 1,2,3-triazoles through a Cu(I)-promoted azide–alkyne 1,3-dipolar cycloaddition between a TMS-protected *C*-alkynyl-glycoside and organic azides. The reaction was accelerated by ultrasound irradiation and the addition of a base was not necessary to obtain the 1,2,3-triazole product. Moreover, further manipulation of the products led to chiral molecules with a *C*-glycoside linkage.

1. Introduction

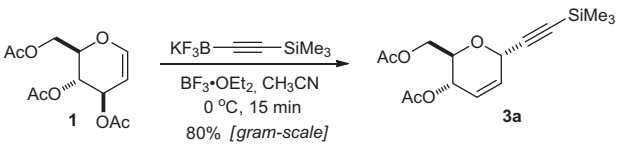
The chemistry and chemical biology of *C*-glycosides has experienced increasing attention due to their potential to serve as carbohydrate analogues resistant to metabolic processes, which might lead to an improved biological profile compared to their *O*-analogues.[1] In addition, *C*-glycosides have also been found embedded in the structure of several bioactive natural products[2] and have served as chiral building blocks for the stereoselective synthesis of optically active compounds.[3] The Huisgen 1,3-dipolar azide alkyne cycloaddition has been the subject of intense research since the discovery by Sharpless[4] and Meldal[5] that the addition of a copper(I) source increases the reaction rate and governs the regioselectivity, favoring 1,4-disubstituted 1,2,3-triazoles. Since then, Cu(I)-promoted azide–alkyne 1,3-dipolar cycloaddition has become commonly used in several areas of science, such as material science,[6] polymer chemistry,[7] nucleoside, nucleotide and DNA modifications,[8] medicinal chemistry,[9] and biomolecular ligation,[10] to cite just a few.[11] In addition, 1,2,3-triazoles have been reported to have important biological activities, including anti-HIV,[12] antitumor,[13] anti-bacterial,[14] and anti-tuberculosis,[15] and can also act as glycosidase,[16] tyrosinase,[17] and serine hydrolase[18] inhibitors.

Not surprisingly, sugar-derived triazoles have also been the subject of research in recent years. The robustness of the triazole linker in the biological environment, which is resistant to hydrolysis, oxidation, and reduction, coupled with their ability to participate in hydrogen-bonding and dipole interactions, has attracted the attention of synthetic carbohydrate chemists, medicinal chemists, and material chemists.[19]

In this context, we now wish to disclose our results on the synthesis of functionalized *C*-glycosides through a Cu(I)-promoted



Scheme 1. Glycosidation reaction favoring the α-stereoisomer.



Scheme 2. Synthesis of the glycosyl alkyne **3a**.

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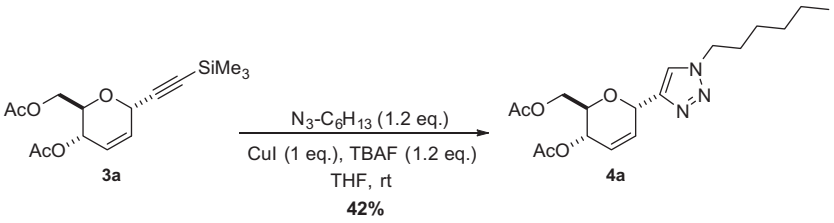
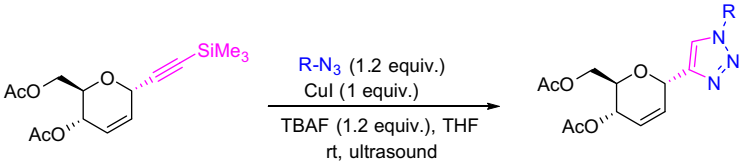
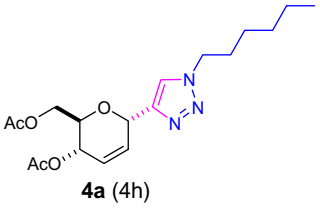
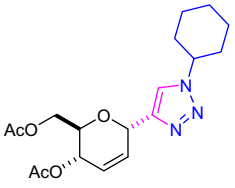
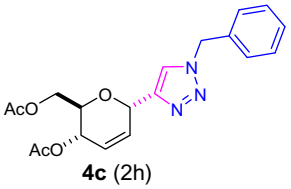
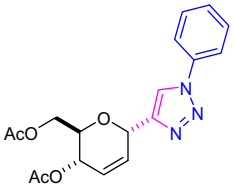
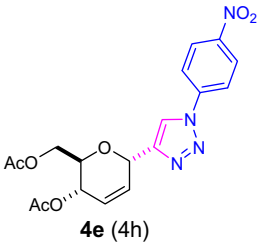


Scheme 3. Cu(I) promoted azide–alkyne cycloaddition.

Table 1
Scope of the cycloaddition reaction



Entry	Azide	Product/Time (h)	Yield[a] (%)
1	C_6H_{13}-N_3	 **4a** (4h)	68
2	*c*-C_6H_{11}-N_3	 **4b** (2h)	63
3	Bn-N_3	 **4c** (2h)	75 (59)[a]
4	Ph-N_3	 **4d** (2h)	51 (48)[a]
5	4-$NO_2C_6H_4$-N_3	 **4e** (4h)	66

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