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

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ABSTRACT

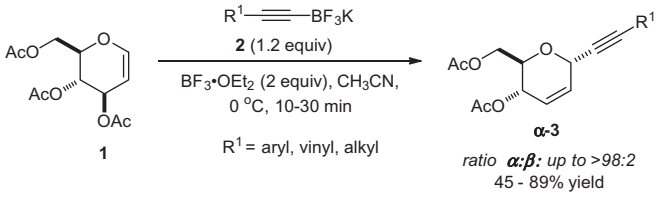
We have developed an efficient method for the synthesis of functionalized *C*-glycosyl 1,2,3-triazoles through a Cu(I)-promoted azide–alkyne 1,3-dipolar cycloaddition between a TMS-protected *C*-alkynyl-glycoside and organic azides. The reaction was accelerated by ultrasound irradiation and the addition 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

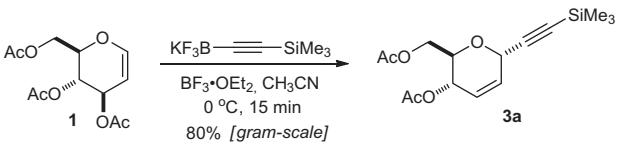
The chemistry and chemical biology of *C*-glycosides has experienced increasing attention due to their potential to serve as carbohydrate analogues resistant to metabolic processes, which might lead to an improved biological profile compared to their *O*-analogues.[1] In addition, *C*-glycosides have 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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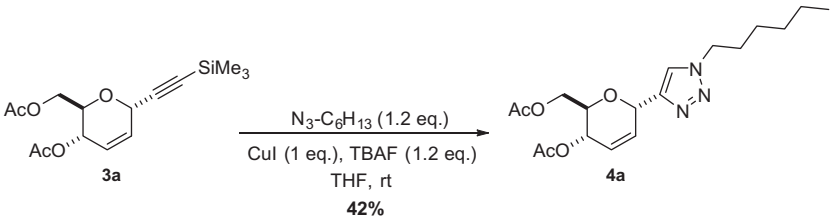
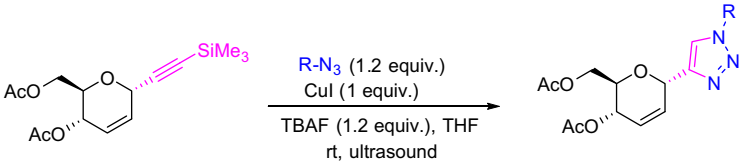
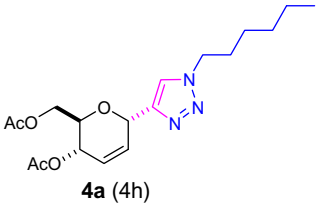
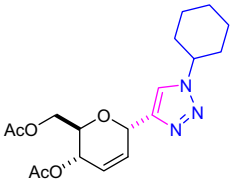
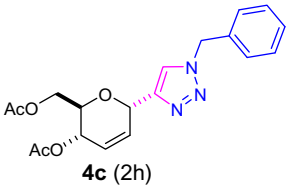
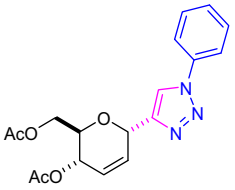
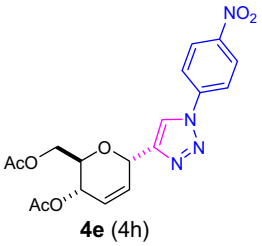


Scheme 3. Cu(I) promoted azide–alkyne cycloaddition.

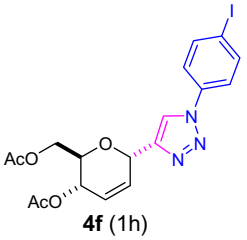
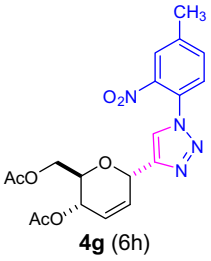
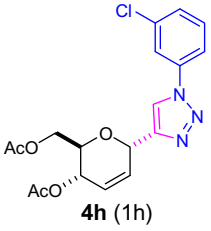
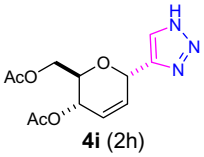
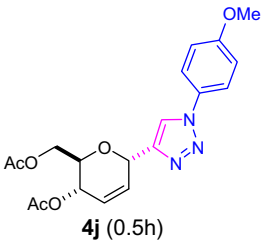
Table 1
Scope of the cycloaddition reaction



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

(*continued on next page*)

Table 1 (*continued*)

Entry	Azide	Product/Time (h)	Yield[a] (%)
6	4-IC_6H_4-N_3	 **4f** (1h)	67
7	4-Me-2-$NO_2C_6H_3$-N_3	 **4g** (6h)	75 (38)[a]
8	3-ClC_6H_4-N_3	 **4h** (1h)	67
9	NaN_3	 **4i** (2h)	NR
10	4-$OMeC_6H_4$-N_3	 **4j** (0.5h)	70

[a] Reactions were carried out with PMDETA as base.

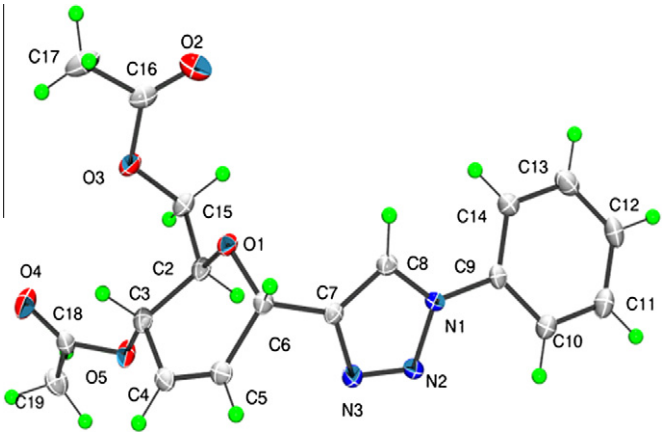


Figure 1. Molecular structure of compound **4d**, showing atom labeling and displacement ellipsoids at the 50% probability level for non-H atoms.

azide–alkyne 1,3-dipolar cycloaddition between a TMS-protected *C*-alkynyl-glycoside and organic azides through 'click chemistry'.

Our approach was based on our recently developed mild and efficient method for the stereoselective synthesis of *C*-alkynyl-glycosides, by the reaction of tri-*O*-acetyl-D-glucal with alkynyltrifluoroborate salts, in the presence of boron trifluoride as the Lewis acid.[20] The glycosidation reaction was found to be very selective, favoring the α-stereoisomer in up to >98:2 dr (Scheme 1).

Initially, the synthesis of the required glycosyl alkyne **3a** was accomplished by our protocol, in a very fast (15 min) and mild reaction in an 80% yield (Scheme 2). The reaction was completely diastereoselective in favor of the α-isomer and could be carried out on the gram-scale, without any noticeable decrease in yield or stereoselectivity.

With the required alkyne in hand, we turned our attention to examining Cu(I) promoted azide–alkyne cycloaddition, initially using hexyl azide as the dipole (Scheme 3). In order to avoid deprotection of the silylated glycosyl alkyne, which would require an

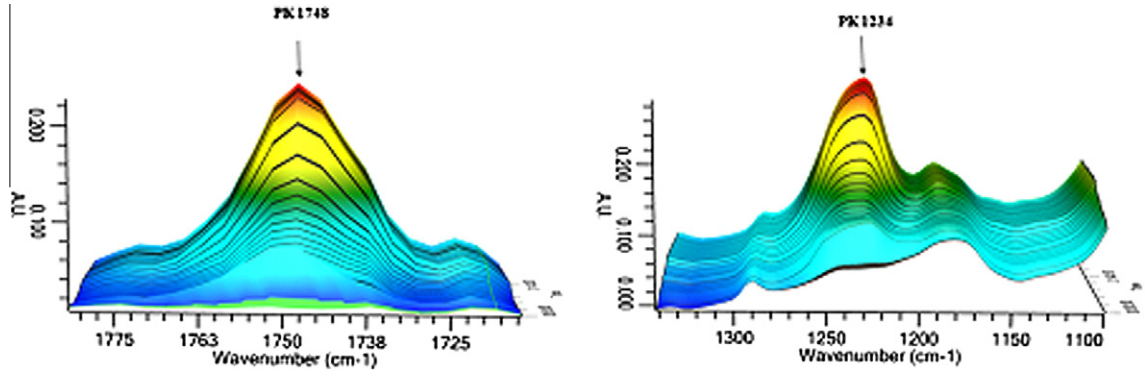
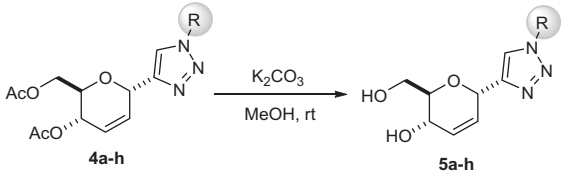
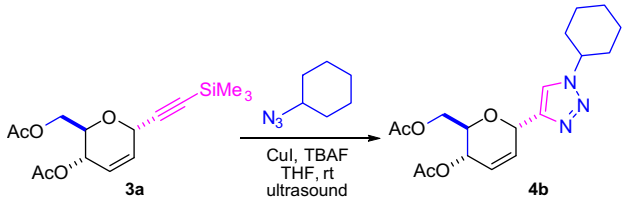


Figure 2. Reaction course followed by in situ IR spectroscopy.

Table 2
Removal of the acetyl protecting groups



Entry	R	Yield (%)
1	C_6H_{13} (**5a**)	95
2	*c*-C_6H_{11} (**5b**)	98
3	Bn (**5c**)	94
4	Ph (**5d**)	94
5	4-$NO_2C_6H_4$ (**5e**)	93
6	4-IC_6H_4 (**5f**)	93
7	4-Me-2-$NO_2C_6H_3$ (**5g**)	90
8	3-ClC_6H_4 (**5h**)	95



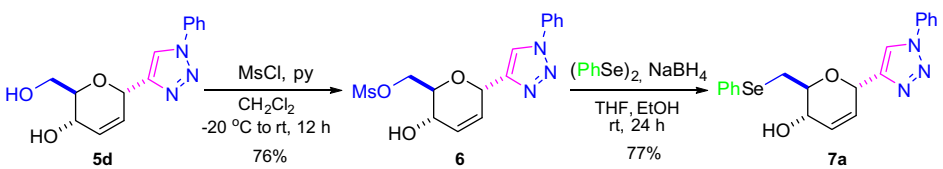
Scheme 4. In situ ReactIR spectroscopy to monitor the formation of the triazole.

additional step, the cycloaddition reaction was performed using the conditions developed by Fiandanese and co-workers, which make use of tetrabutyl ammonium fluoride to promote the removal of the silyl protecting group in situ.[21] Moreover, the reaction was carried out using copper iodide as the Cu(I) source and THF as the solvent. Applying these conditions to our system resulted in the formation of the *C*-glycosyl triazole in a moderate 42% yield.

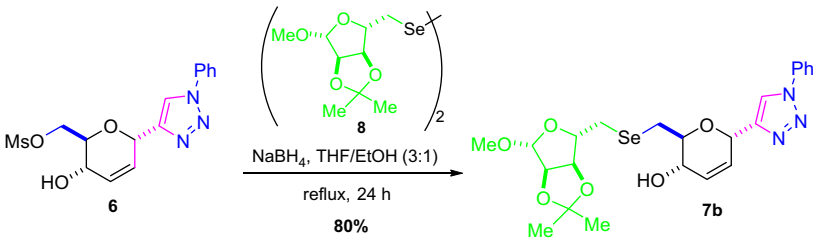
After some experimentation, we found that better results were achieved under ultrasound irradiation,[22,23] leading to an improvement in the yield of compound **4a** to 68% (Table 1, entry 1). The beneficial effect of sonication on the azide–alkyne cycloaddition has already been observed in our laboratory[24] and by others.[25] The extension of these conditions to a broader range of azides allowed the synthesis of a number of chiral 1,2,3-triazoles in good yields under mild reaction conditions. When aliphatic azides were employed as substrates, the corresponding products were obtained in good yields (entries 1–3). Aromatic azides were also tested as substrates for Cu(I)-promoted cycloaddition; when phenylazide was employed, the corresponding triazolyl glucoside was obtained in a moderate 51% yield (entry 4). Conversely, substituted aromatic azides, particularly those with electron withdrawing groups, resulted in better yields (entries 5–8). The best result was achieved with a trisubstituted aryl azide possessing a nitro group *ortho* to the azide functionality (entry 7). In contrast to these results, when sodium azide was employed as the 1,3-dipole, the desired product was not obtained and only deprotection of the silyl group was observed, and ethynyl *C*-glucoside was partially recovered from the reaction (30%) (entry 9). Attempts to improve the yield by the addition of an amine base were also pursued. Therefore, based on the work of Fiandanese et al., we choose to use *N*,*N*,*N*′,*N*′,*N*″-pentamethyldiethylenetriamine (PMDETA) as the amine. Unfortunately, for the cases studied, the presence of the amine resulted in a deleterious effect on the reaction outcome and a decrease in the yield was observed (see entries 3, 4, and 7) or the product was not formed at all (entry 9).

As suitable crystals of **4d** were obtained, its absolute configuration was confirmed by X-ray diffraction.[26] As shown in Figure 1, the chirality of C2, C3, and C6 was *R*, *S*, and *S*, respectively. In the crystal, the molecules were linked by C–H···O, C–H···N, and C–H···π interactions, the latter involving the triazole moiety. The compound crystallizes in space group $P2_1$ with only one independent molecule in the asymmetric unit. The diffraction measurements were carried out with Cu Kα radiation and the absolute structure was determined using 1591 Friedel pairs, obtaining a Flack parameter of −0.09(15).[27]

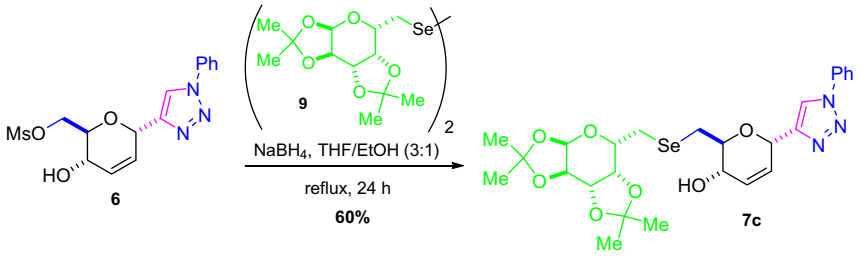
In order to investigate the reaction outcome, in situ ReactIR spectroscopy was employed to monitor the formation of the



Scheme 5. Synthesis of seleno-carbohydrate derivative.



Scheme 6. Synthesis of seleno-(D)-galactose pyranoside.



Scheme 7. Synthesis of seleno-(D)-ribose pyranoside.

triazole product, which is a useful tool for monitoring and optimizing reaction processes.[28] The reaction between **3a** and cyclohexyl azide was chosen for this investigation (Scheme 4).

During the experiment, it was found that the ν_{CO2} of the carbonyl group could be easily observed. After the addition of TBAF, there was a rapid increase in this band at 1748 cm^{-1}. The surface at 1234 cm^{-1} could be assigned to a vibrational stretching of carbon–nitrogen in the triazole ring, indicating the formation of the product. It is important to point out that this formation reached a maximum in 45 min (Fig. 2).

Our next step was directed toward the functional group manipulation of the triazole-glucosides. Thus, the removal of the acetyl protecting groups was achieved by treatment with potassium carbonate in methanol, under mild reaction conditions, leading to the corresponding product possessing two free hydroxy groups (Table 2). For all cases studied, the reaction was very efficient and the deprotected products were obtained in excellent yields. These chiral carbohydrate-derived compounds were interesting polyfunctionalized molecules and were amenable to further transformations. Selective reactions could be performed at the diol moiety, since one of the hydroxy groups was primary and the other was a secondary allylic alcohol. Moreover, the internal allylic double bond could be selectively functionalized with several reagents leading to two new additional stereogenic centers and an even more functionalized molecule.

In an effort to further explore the potential of the glucal derivatives, we sought to activate the primary hydroxy group. Initial attempts were directed toward tosylation using TsCl; however, the desired product was not obtained despite several experiments varying the solvent, base, and temperature. Gratifyingly, when we changed the activating agent to MsCl, the selective mesylation of the primary hydroxyl in **5d** occurred and the corresponding product was obtained in a 76% yield in a clean reaction (Scheme 5). Further, in connection with the growing importance of the synthesis of small molecules containing an organoselenium moiety, due to their biological and pharmacological properties,[29] we sought to replace the mesylate leaving group with a selenium nucleophile. Therefore, the reaction of the mesylate **6** with a phenylselenide nucleophile resulted in a substitution reaction, leading to the corresponding seleno-carbohydrate **7a** in a 77% isolated yield.

In order to obtain some insight into why the tosylation reaction did not occur, a calculation of the reaction pathway and the structure of the transition states for TsCl and MsCl was performed (for computational details, see the Supplementary data). The Intrinsic Reaction Coordinate (IRC) calculations showed that the transition states, for both tosyl and mesyl, had very similar structures (Figs. S1 and S2), with the chlorine atom making a S···Cl and three C–H···Cl interactions. As can be seen in Tables S1 and S2, according to the NBO (Natural Bond Orbital) analysis, the S···Cl interaction was stronger in the transition state of the tosylate than in the mesylate, thus making it easier for the chlorine atom to leave. Moreover, the non-bonded S···Cl distance after attaining the threshold gradient value in the IRC for the mesylate case was 5.02 Å while for the tosylate this was 3.24 Å (Figs. S3 and S4), indicating that there was still some interaction between these atoms, thus precluding the continuation of the reaction toward tosylation.

With the success achieved in the introduction of an organoselenium moiety in the triazole-glucoside framework, we decided to explore the same strategy using selenium nucleophiles of more complex structure, such as those derived from other sugars.[30] Therefore, reductive cleavage of diselenides **8** and **9**, derived from D-galactose and D-ribose, followed by trapping with the glucal-derived mesylate **6**, resulted in clean substitution reactions and the corresponding products were isolated in good yields (Schemes 6 and 7). The reaction worked with both pyranoside and furanoside selenium nucleophiles. It is worth noting that a significant increase in structural complexity could be achieved by a simple synthetic strategy. The obtained products displayed a disaccharide-like structure in which two different sugar units were connected by a selenium atom.

2. Conclusion

In summary, 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.

Acknowledgements

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.01.102.

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