Tetrahedron Letters 56 (2015) 5521–5524

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A metal free aqueous route to 1,5-disubstituted 1,2,3-triazolylated monofuranosides and difuranosides

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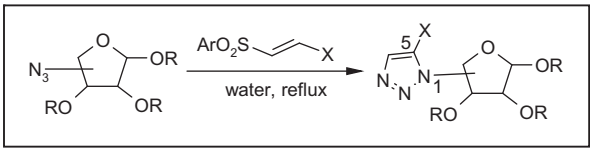
ARTICLE INFO

Article history:
Received 19 June 2015
Revised 9 August 2015
Accepted 11 August 2015
Available online 14 August 2015

Keywords:
1,5-Disubstituted 1,2,3-triazole
Furanoside
Vinylsulfone
Aqueous
Metal free

ABSTRACT

Vinyl sulfones and vinyl sulfone-modified carbohydrates were subjected to 1,3-dipolar-cycloaddition reactions with four different azidofuranosides having azido groups at the C5 and C6-positions under refluxing conditions in aqueous media without any metal catalyst to afford the 1,5-disubstituted 1,2,3-triazolylated monofuranosides and difuranosides in high yields. These syntheses of 1,5-disubstituted triazolylated monosaccharides as well as 1,5-disubstituted 1,2,3-triazole linked disaccharides open up a new possibility of connecting furanosides with a stable-triazole backbone.



Cu(I) catalyzed azide–alkyne cycloaddition (CuAAC) reaction has been widely used for the synthesis of 1,4-disubstituted 1,2,3-triazoles (1,4-DTs).[1] Since carbohydrate molecules are widely used as a major source of chiral resources[2] and are increasingly considered as a major source of drug molecules,[3] CuAAC has been widely applied in the synthesis of 1,4-DT functionalized carbohydrate derivatives.[4] Several 1,4-disubstituted 1,2,3-triazolylated furanosyl monosaccharides have also been prepared using this strategy (Fig. 1).[5a–c] For example, the sugar triazoles **1a**–**e**, **2a**–**e**, **3a**–**e** and **4a**–**e** were evaluated against an avirulent strain, *Mycobacterium tuberculosis H37Ra*, and a virulent strain, *M. tuberculosis H37Rv*. Compound **4e** of this series displayed a moderate antitubercular activity with an MIC of 12.5 μg/mL.[5a,b] Compound **5** has also shown antitubercular activity.[5c] The 1,4-DT linked disaccharides **6a**–**c** were screened for their enzyme inhibitory activities against α-glucosidase, glycogen-phosphorylase and glucose-6-phosphatase.[5d]

Although the CuAAC reaction[6] triggered new developments in synthetic chemistry as well as biology[7] and material sciences,[8] efficient and general synthetic approaches towards 1,5-disubstituted 1,2,3-triazoles (1,5-DTs) have achieved limited success so far.[9] The methods available for the synthesis of 1,5-DTs **7** by different groups are summarized in Scheme 1. Amongst all the metal-mediated routes to 1,5-DTs, RuAAC remains the most popular method,[10] although the reaction conditions are much less efficient than the 'Click' reaction.[6b,11] Moreover, the possibility of toxicity of residual metal in metal-mediated triazolylation led to the quest for metal-free routes to 1,5-DTs which is also limited in number.[12,13] It is therefore not surprising that in general, the world-wide research is overwhelmingly biased towards the synthesis and applications of 1,4-DTs.

The situation is far worse in the area of triazolylation of carbohydrates. As a result there are only few scattered reports on the synthesis of 1,5-DT functionalized carbohydrates.[14–16] However, to the best of our knowledge there are no reports on furanosides functionalized with 1,5-DTs at C5 or C6 although many of the corresponding 1,4-triazolylated carbohydrates are known having

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http://dx.doi.org/10.1016/j.tetlet.2015.08.030
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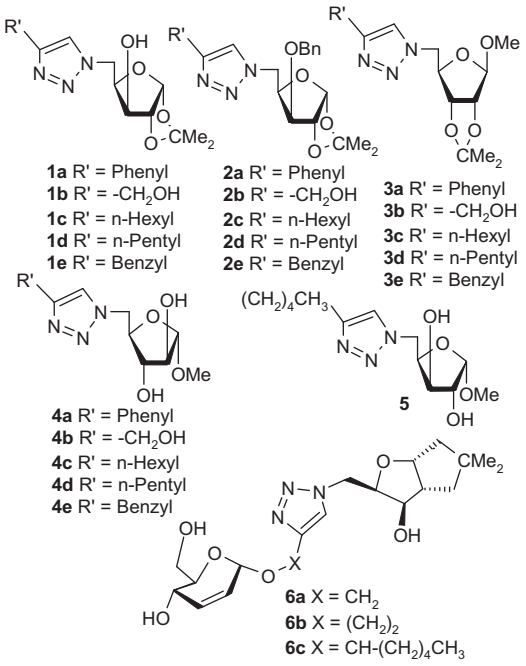
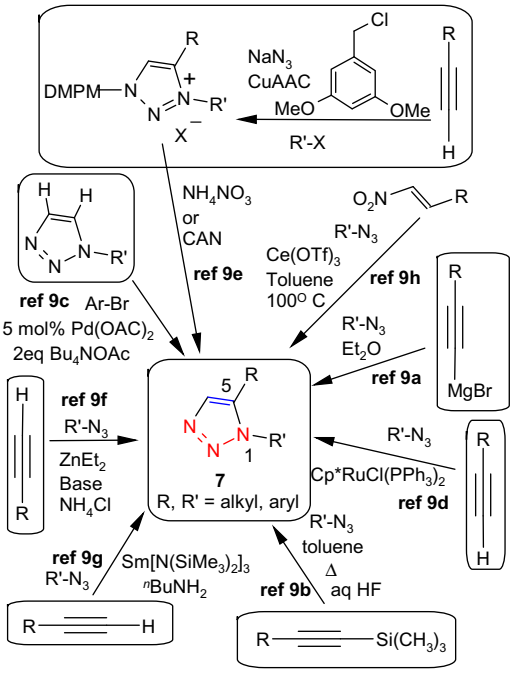


Figure 1. C5-functionalized 1,4-DT modified monosaccharides and disaccharides.

interesting biological properties (Fig. 1).[5] Surprisingly, in spite of the availability of propargylated carbohydrates,[17] the 1,5-DT functionalized carbohydrates are separated from a mixture of 1,4- and 1,5-DTs which are obtained by refluxing corresponding acetylenes and azides.[14c–e] It appears that, even in the post 'Click' era, the separation of isomers was much easier than using any of the methods reported in Scheme 1. For example, the furanosides **8**[14e] and **9**[14e] depicted in Figure 2 were synthesized by refluxing the corresponding azides and alkynes, followed by the separation of 1,4- and 1,5-regioisomers.



Scheme 1. Schematic representation of various methods for the synthesis of 1,5-DTs.

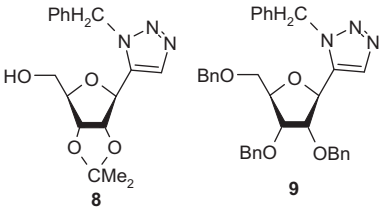


Figure 2. 1,5-DT modified carbohydrates extracted from the mixture of 1,4- and 1,5-DTs.

Earlier we had developed easy methods for the synthesis of a wide range of vinyl sulfone-modified carbohydrates.[18] While vinyl sulfoxides were considered as acetylene equivalent,[19] we have shown that vinyl sulfones also effectively act as acetylene equivalent in the 1,3-dipolar cycloaddition reaction with organic azides to afford regioselectively 1,5-DTs.[20]

Moreover, vinyl sulfones[18,21] are easily accessible from a wide variety of 1,2-diols, olefins, epoxides, dibromides and aldehydes which as a strategy is more flexible than constructing the propargyl group on carbohydrates only from aldehydes.[17b] We therefore selected a group of azidofuranosides **10**–**13**[5a,22] (Fig. 3) and separately reacted those with two simple vinyl sulfones **14a**–**b**[20b] (Fig. 3). Thus a mixture of a vinyl sulfone and a azidofuranoside was heated under reflux in water to afford 1,5-triazolylated monofuranosides **16**–**19** (Scheme 2). This method incorporated the triazolyl group via its N-1 position at the C-5 or C-6 of the pentofuranosides and hexofuranosides at ease.

A more challenging task is to construct the triazolyl ring using the C-5 and C-6 positions of the carbohydrate. To this end, we reacted the same group of azido furanosides with vinyl sulfones[20b] derived from gluco and allo furanosides **15a**,**b** (Fig. 3) and **15c** (Fig. 3) in refluxing water. In this case also triazolyl-linked difuranosides **20**–**23** were formed in high yields (Scheme 3). We were unable to detect any 1,4-isomer from these reactions either during purification (TLC-analysis) or in the ^{1}H NMR spectra of the final products. To unambiguously establish the structures of some of these 1,5-regioisomers, we synthesized the 1,4-regioisomers **26**–**28** (Fig. 4; See SI, Scheme 1) of some of the 1,5-DT modified monosaccharides **16**–**19** (Scheme 2) with the help of the well known CuAAC route.[1]

However, we also used the ^{13}C NMR data for establishing the structures using reported strategies.[14d,23] Thus, the chemical shift

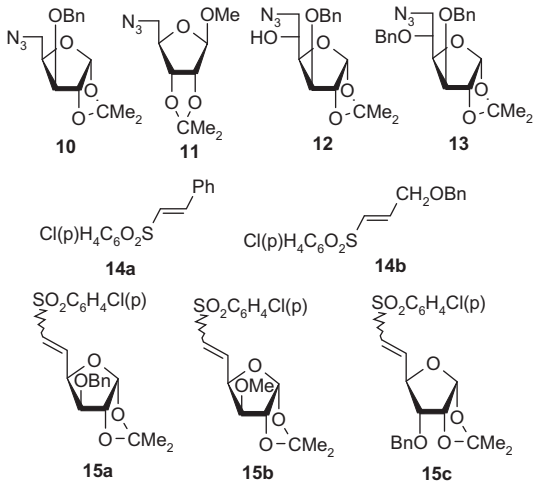


Figure 3. Azidofuranosides and vinyl sulfones used for the synthesis of 1,5-DT modified mono- and disaccharides.