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RAPID ACCESS TO GLUCOPYRANOSYL-1,2,3-TRIAZOLES *VIA* Cu(I)-CATALYZED REACTIONS IN WATER

Rakesh A. Akula, David P. Temelkoff, Nicole D. Artis, and Peter Norris*

Department of Chemistry, Youngstown State University, 1 University Plaza, Youngstown, OH 44555, U.S.A.

Abstract – 1-Azido-1-deoxy-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose reacts with various terminal alkynes in the presence of $CuSO_4$/ascorbic acid in water to give the corresponding 1,4-disubstituted 1,2,3-triazoles, which are isolated in high yield and purity by simply filtering the precipitate from the reaction mixture. Several sugar-derived acetylenes react similarly to yield triazole-linked disaccharide analogs.

With the growing appreciation of the roles that sugars play in numerous biological events there is a demand for new compounds that may serve as tools with which to study such processes. Impressive advances have been made in the synthesis of *O*-glycosides, as well as *C*-glycosides and *N*-glycosides, which serve as *glycomimetic* analogs of parent *O*-glycosides.[1] Numerous *C*-glycosidic structures are found in nature and the *N*-glycoside motif appears in the nucleic acids and in *N*-linked glycopeptides.[2]

The control of stereochemistry during *O*-glycosylation remains one of the ultimate challenges in synthetic carbohydrate chemistry, and similar difficulties are encountered in *C*-glycoside formation. There are few truly general approaches to each of these types of compound. The situation is somewhat different in the *N*-glycoside field due to the fact that the most common precursors, i.e. glycosyl azides, are usually prepared by *stereospecific* bimolecular displacement of a glycosyl halide, many of which are available in diastereomerically pure form.[3]

The formation of 1,2,3-triazoles at the anomeric position of carbohydrates has traditionally involved the Huisgen 1,3-dipolar cycloaddition[4] between a glycosyl azide and an alkyne partner,[5] however the utility of the process has been limited due to slow reactions with unactivated alkynes and the formation of isomeric

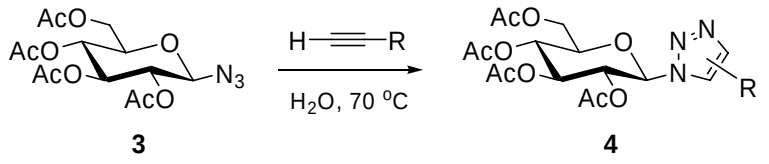
mixtures of 1,4- and 1,5-disubstituted triazole products. Since glycosyl-1,2,3-triazoles (**2**, Figure 1) could potentially serve as mimics of glycosyl amides (**1**, Figure 1) we were interested in applying recently developed methods for 1,2,3-triazole synthesis based on Cu(I) catalysis.

Sharpless and colleagues have suggested the 1,2,3-triazole ring as a useful way of conjugating biologically active groups.[6] Meldal and coworkers reported the use of Cu(I) halides to form peptido-1,4-substituted 1,2,3-triazoles *regiospecifically*,[7] and very shortly afterwards Sharpless and Fokin published their work on the use of $CuSO_4$ in azide-acetylene "ligations" in which the Cu(I) catalyst is generated by reaction of $CuSO_4$ with sodium ascorbate.[8] Aside from the affordability of this reagent mixture, the fact that the reactions were performed in aqueous medium made this system extremely attractive for rapid glycosyl-1,2,3-triazole synthesis.

Figure 1

There have been several recent reports dealing with copper(I)-catalyzed 1,2,3-triazole synthesis in carbohydrate systems. Santoyo-González and colleagues have used an organic-soluble catalyst to produce a wide variety of triazole-linked neoglycoconjugates,[9] and Gin and coworkers have used similar chemistry to build cyclodextrin analogs.[10] We now communicate our work on the rapid, regiospecific synthesis and isolation of various glucosyl-1,4-disubstituted 1,2,3-triazoles using the Sharpless $CuSO_4$/ascorbic acid system using water as the solvent.

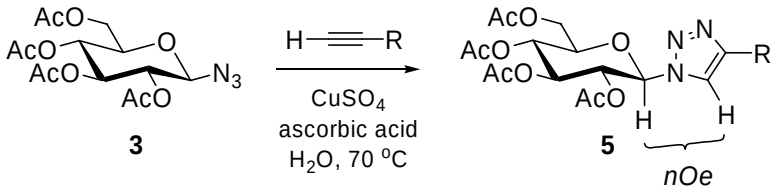
1-Azido-1-deoxy-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose (**3**, Eq. 1) is available on large scale[11] and is insoluble in water at room temperature. In initial experiments to determine if co-solvents where needed for reactions with various acetylenes, it was found that uncatalyzed reactions were possible but were very slow (up to four days with 1-ethynyl-3-fluorobenzene) and resulted in the isolation of mixtures of 1,4- and 1,5-disubstituted triazoles (**4**, Eq. 1). No co-solvent was necessary and the products readily precipitated and could be isolated by filtration.



Equation 1

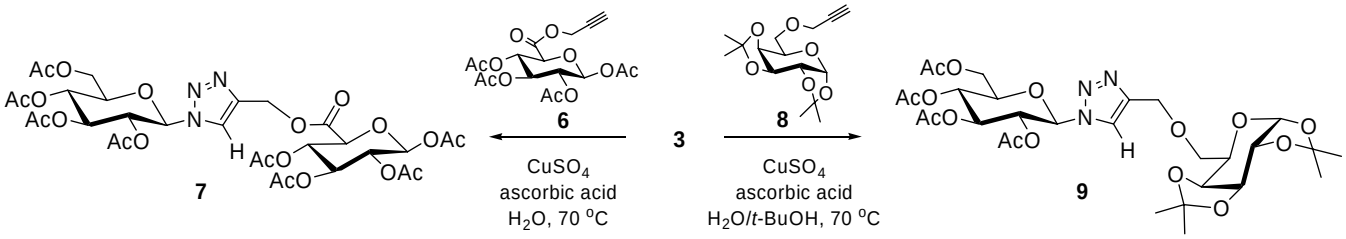
With $CuSO_4$/ascorbic acid the reactions of azide (**3**) with various terminal acetylenes were complete within eight hours and the products, isolated by filtration, were found to be a single triazole (**5**, Eq. 2, Table 1).[12]

Purity was >90% in all cases as judged by ^{1}H NMR spectra. The 1,4-disubstituted triazole products correspond to the major isomer formed in the uncatalyzed reactions, which is the accepted outcome for such conventional Huisgen dipolar cycloadditions.[13,14] Additionally, nOe experiments on triazole **5f** (R = Ph) show clear interaction between H-1 of the pyranose ring and the proton attached to the triazole ring (Eq. 2), which would be unlikely if the product where the 1,5-isomer.



Equation 2

The simplicity of this method suggests it would be useful for the synthesis of libraries of triazole-linked oligosaccharide analogs.[15] To illustrate this, reaction of azide (**3**) with D-glucuronic acid-derived alkyne (**6**) (Scheme 1) in water in the presence of $CuSO_4$/ascorbic acid gave a single triazole (**7**, Scheme 1) in 76% yield,[16] which again was isolated in very pure form simply by filtration and drying. A related D-galactose-derived alkyne (**8**, Scheme 1) required the use of *t*-BuOH as co-solvent due to the low solubility of isopropylidene derivatives versus acetate-protected sugars. However, the product triazole (**9**, Scheme 1) could be isolated in 84% yield by evaporating most of the *t*-BuOH and allowing the product to precipitate from the remaining aqueous mixture.[18]



Scheme 1

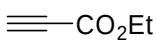
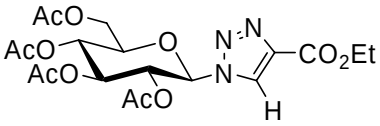
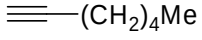
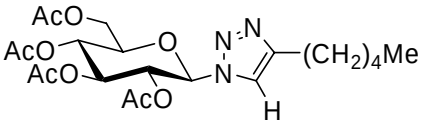
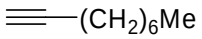
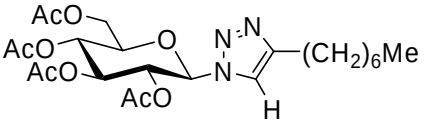
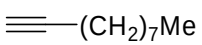
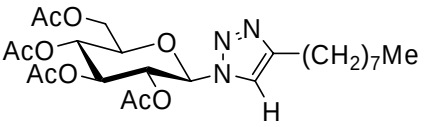
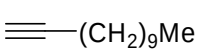
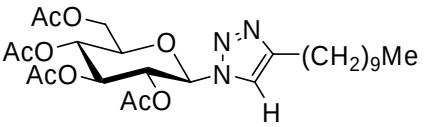
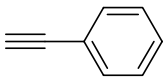
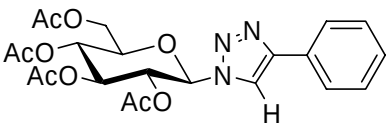
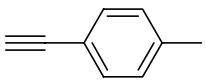
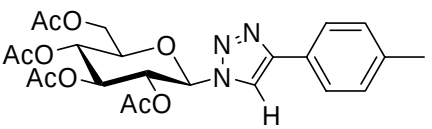
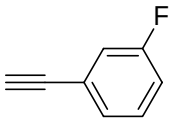
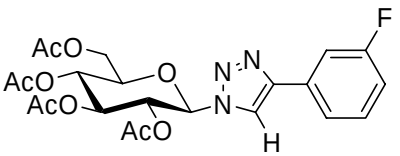
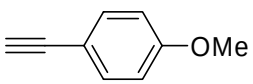
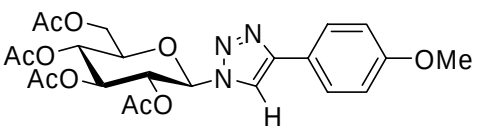
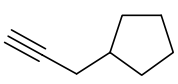
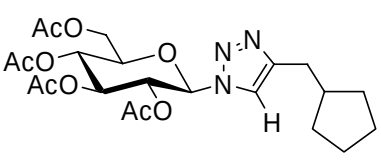
ACKNOWLEDGEMENTS

The American Chemical Society's Project SEED is thanked for a stipend for N.D.A. This work was sponsored by the National Institutes of Health (R15-AI053112-01).

REFERENCES AND NOTES

1. For recent reviews in *O*-glycoside, *C*-glycoside, and glycosyl amino acid synthesis see 'Carbohydrates,' ed. by H. M. I. Osborn, Elsevier, Oxford, UK, 2003.
2. B. G. Davis, *Chem. Rev*., 2002, **102**, 579.

Table 1. Alkynes used in this work and yields for resultant glucosyl-1,2,3-triazoles.

Entry	Alkyne	Glucosyl triazole product	%Yield[a]
a			92
b			89
c			81
d			78
e			94
f			85
g			82
h			61
i			79
j			80

[a]Satisfactory ^{1}H NMR, ^{13}C NMR, and HRMS spectral data were obtained for all compounds.

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12. Typical procedure for synthesis of 1-glucopyranosyl-4-substituted 1,2,3-triazoles (**5**): Azide (**3**) (1.0 g, 2.68 mmol), $CuSO_4$ (0.01 g, 0.04 mmol), ascorbic acid (0.1 g, 0.56 mmol) and phenylacetylene (0.3 mL, 2.70 mmol) were heated together in water (15 mL) at 70 ^oC for 8 h. The mixture was cooled to rt and then in an ice bath. The solid was filtered and washed with water (10 mL) and methanol (10 mL) to leave a pale yellow powder (1.08 g, 85%), which was >90% pure by ^1H NMR spectrum and homogenous by TLC. Recrystallization from 95% ethanol gave **5f** as a fluffy white solid: mp 198-202 ^oC; $[\alpha]_D$ -85.8^o (*c* 1.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 1.88, 2.03, 2.07, 2.08 (4 x s, 3H each, 4 x $COCH_3$), 4.03 (m, 1H, H-5), 4.15 (dd, 1H, *J* = 1.8, 12.5 Hz, H-6), 4.32 (dd, 1H, *J* = 5.1, 12.6 Hz, H-6'), 5.27 (t, 1H, *J* = 9.5 Hz, H-2), 5.44 (t, 1H, *J* = 9.3 Hz, H-3), 5.52 (t, 1H, *J* = 9.5 Hz, H-4), 5.93 (d, 1H, *J* = 9.2 Hz, H-1), 7.25-7.84 (m, 5H, Ar-H), 8.00 (s, 1H, triazole-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 21.8 (double intensity), 22.0, 62.7, 68.9, 71.3, 73.9, 76.3, 86.9, 118.8, 126.9, 129.6, 129.9, 130.9, 149.5, 169.8, 169.9, 170.3, 170.8; HRMS calcd for $C_{22}H_{25}N_3O_9$ (+Na): 498.1488, found 498.1451.[14]
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14. Triazole (**5f**) has been reported previously: M. T. Garcia-Lopez, G. Garcia-Munoz, J. Iglesias, and R. Madronero, *J. Heterocycl. Chem*., 1969, **6**, 639.
15. S. Sabesan, 'Preparation of Triazole-linked Oligosaccharides *via* Cycloaddition of Alkyne with Azide Sugars.' U.S. Patent 6,664,399, December 16, 2003 (*Chem. Abstr*., 2004, **140**, 667).
16. Alkyne (**6**) was prepared in 95% yield by treating 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranuronosyl chloride[18] with propargyl alcohol in pyridine: mp 138-141 ^oC; $[\alpha]_D$ +10.8^o (*c* 1.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 2.04, 2.05, 2.07, 2.13 (4 x s, 3H each, 4 x $COCH_3$), 2.53 (t, 1H, *J* = 2.5 Hz, alkyne-H), 4.24 (d, 1H, *J* = 9.5 Hz, H-5), 4.71 (m, 2H, CH_2), 5.15 (dd, 1H, *J* = 7.7, 9.0 Hz, H-2), 5.25

(t, 1H, *J* = 9.5 Hz, H-4), 5.33 (t, 1H, *J* = 9.0 Hz, H-3), 5.78 (d, 1H, *J* = 7.7 Hz, H-1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8 (triple intensity), 22.0, 54.8, 69.9, 71.2, 72.8, 73.8, 77.2, 77.5, 92.3, 166.7, 169.7, 170.1, 170.4, 170.8; HRMS calcd for $C_{17}H_{20}O_{11}$ (+Na): 423.0903, found 423.0907. Triazole (**7**) was prepared by heating azide (**3**) (746 mg, 2.0 mmol) and alkyne (**6**) (800 mg, 2.0 mmol) with $CuSO_4$ (0.025 mL of a 1M aqueous solution) and ascorbic acid (0.25 mL of a 1M aqueous solution) in water (15 mL) at 70 ^{o}C for 12 h. After cooling to rt the precipitate was collected on a glass frit and washed with cold methanol. Triazole (**7**) (1.2 g, 76%) was isolated as a tan solid: mp 204-208 ^{o}C; $[\alpha]_D$ -5.8^{o} (*c* 1.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, *glu* = glucopyranose ring, *gluA* = glucuronic acid ring) δ 1.89, 1.99, 2.01, 2.04, 2.08, 2.10, 2.12 (7 x s, total 24 H, 8 x $COCH_3$), 3.99 (m, 1H, H-5$_{glu}$), 4.14 (dd, 1H, *J* = 2.2, 12.9 Hz, H-6$_{glu}$), 4.20 (d, 1H, *J* = 9.7 Hz, H-5$_{gluA}$), 4.29 (dd, 1H, *J* = 4.9, 12.6 Hz, H-6'$_{glu}$), 5.11-5.48 (m, 8H, H-2$_{glu}$, H-2$_{gluA}$, H-3$_{glu}$, H-3$_{gluA}$, H-4$_{glu}$, H-4$_{gluA}$, -OC<u>H</u>$_2$-triazole), 5.76 (d, 1H, *J* = 7.7 Hz, H-1$_{gluA}$), 5.88 (d, 1H, *J* = 9.0 Hz, H-1$_{glu}$), 7.89 (s, 1H, triazole-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 21.7, 21.8 (quadruple intensity), 21.9, 22.0, 59.9, 62.6, 68.7, 69.8, 71.2, 71.3, 72.9, 73.7, 73.8, 76.2, 86.8, 92.3, 124.0, 143.0, 167.2, 169.7, 169.8, 170.1, 170.2, 170.5, 170.7, 170.8, 171.4; HRMS calcd for $C_{31}H_{39}N_3O_{20}$ (+Na): 796.2025, found 796.2031.

17. Alkyne (**8**) was prepared in 80% yield by treating 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose with propargyl bromide and KOH in MeCN: mp 50-54 ^{o}C; $[\alpha]_D$ -3.2^{o} (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33, 1.35, 1.46, 1.55 (4 x s, 3H each, 4 x CH_3), 2.44 (t, 1H, *J* = 2.0 Hz, alkyne-H), 3.67 (dd, 1H, *J* = 7.1, 10.1 Hz, H-6), 3.78 (dd, 1H, *J* = 5.2, 10.2 Hz, H-6'), 4.00 (m, 1H, H-5), 4.17-4.33 (m, 4H, H-2, H-4, propargyl CH_2), 4.61 (dd, 1H, *J* = 2.3, 8.0 Hz, H-3), 5.55 (d, 1H, *J* = 5.1 Hz, H-1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.7, 26.1, 27.2, 27.3, 59.6, 67.8, 69.8, 71.5, 71.7, 72.2, 75.8, 80.7, 97.4, 109.6, 110.3; HRMS calcd for $C_{15}H_{22}O_6$ (+Na): 321.1314, found 321.1297. Triazole (**9**) was formed in a similar fashion to compound (**7**) with the addition of *t*-BuOH as a co-solvent. Thus, azide (**3**) (2.61 g, 7.0 mmol), alkyne (**8**) (2.09 g, 7.0 mmol), $CuSO_4$ (0.05 mL of a 1M aqueous solution) and ascorbic acid (0.5 mL of a 1M aqueous solution) in water were heated in a mixture of water (10 mL) and *t*-BuOH (10 mL) at 70 ^{o}C for 90 min. After evaporating the *t*-BuOH the precipitate was filtered and washed with cold water to give triazole (**9**) (3.97 g, 84%) as a colorless powder: mp 160-163 ^{o}C; $[\alpha]_D$ -44.3^{o} (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, *glu* = glucopyranose ring, *gal* = galactopyranose ring) δ 1.34, 1.35, 1.45, 1.54 (4 x s, 3H each, 4 x CH_3), 1.88, 2.04, 2.08, 2.09 (4 x s, 3H each, 4 x $COCH_3$), 3.68 (dd, 1H, *J* = 7.0, 10.1 Hz, H-6$_{gal}$), 3.74 (dd, 1H, *J* = 5.6, 10.2 Hz, H-6'$_{gal}$), 4.00 (m, 2H, H-5$_{glu}$, H-5$_{gal}$), 4.12 (dd, 1H, *J* = 1.5, 12.5, H-6$_{glu}$), 4.25-4.33 (m, 3H, H-6'$_{glu}$, H-2$_{gal}$, H-3$_{gal}$), 4.61 (dd, 1H, *J* = 2.2, 7.9 Hz, H-4$_{gal}$), 4.68 (m, 2H, -OC<u>H</u>$_2$-triazole), 5.24 (t, 1H, *J* = 9.4 Hz, H-4$_{glu}$), 5.40 (m, 2H, H-2$_{glu}$, H-3$_{glu}$), 5.56 (d, 1H, *J* = 4.9 Hz, H-1$_{gal}$), 5.89 (d, 1H, *J* = 8.8 Hz, H-1$_{glu}$), 7.84 (s, 1H, triazole-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 21.7, 21.8, 21.9, 25.7,

26.1, 27.2, 27.3, 62.7, 65.8, 67.9, 68.8, 70.5, 71.4, 71.6, 71.7, 72.2, 73.8, 76.1, 86.7, 97.4, 109.6, 110.3, 122.0, 146.9, 169.8, 170.3, 170.8, 171.4; HRMS calcd for $C_{29}H_{41}N_3O_{15}$ (+Na): 694.2435, found 694.2433.

18. M. Tosin and P. V. Murphy, *Org. Lett*., 2002, **4**, 3675.