

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

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Abstract – 1-Azido-1-deoxy-2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranose reacts with various terminal alkynes in the presence of CuSO₄/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 cycloaddition⁴ 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.

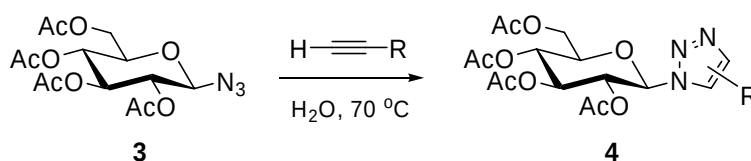
Sharpless and colleagues have suggested the 1,2,3-triazole ring as a useful way of conjugating biologically active groups.⁶ Meldal and coworkers reported the use of Cu(I) halides to form peptido-1,4-substituted 1,2,3-triazoles *regiospecifically*,⁷ and very shortly afterwards Sharpless and Fokin published their work on the use of CuSO₄ in azide-acetylene “ligations” in which the Cu(I) catalyst is generated by reaction of CuSO₄ 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 CuSO₄/ascorbic acid system using water as the solvent.

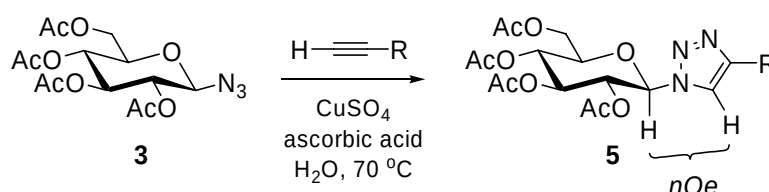
1-Azido-1-deoxy-2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranose (**3**, Eq. 1) is available on large scale¹¹ and is insoluble in water at room temperature. In initial experiments to determine if co-solvents were needed for reactions with various acetylenes, it was found that uncatalyzed reactions were possible 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

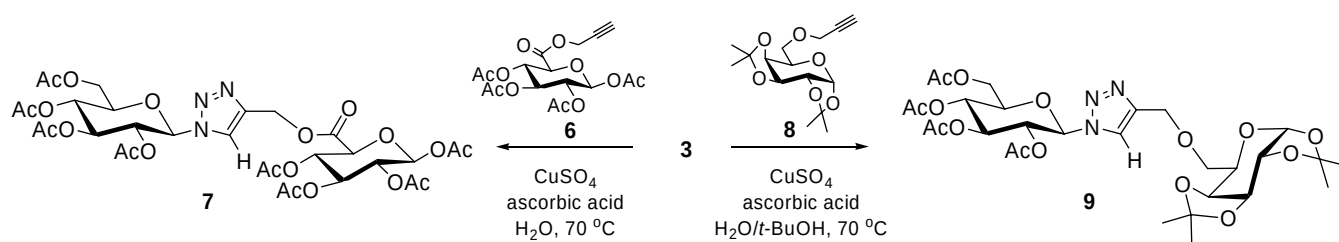
With CuSO₄/ascorbic acid the reactions of azide (**3**) with various terminal acetylenes were complete within eight hours and the products, isolated by filtration, were found to be a single triazole (**5**, Eq. 2, Table 1).¹²

Purity was >90% in all cases as judged by ^1H 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 were 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

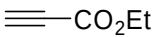
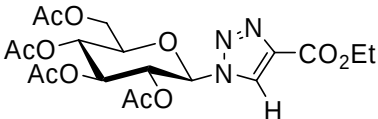
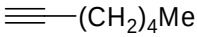
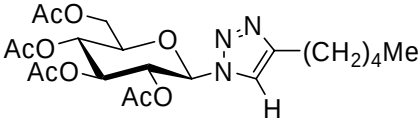
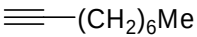
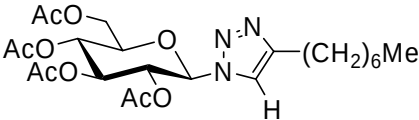
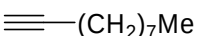
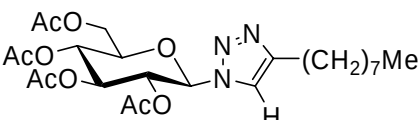
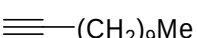
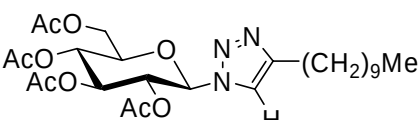
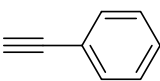
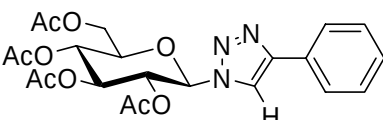
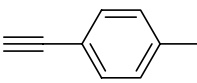
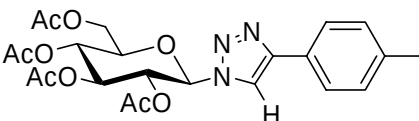
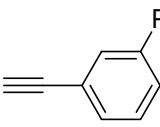
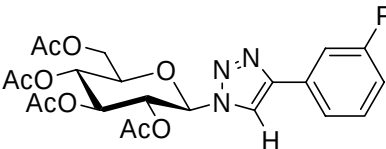
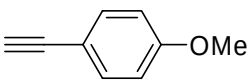
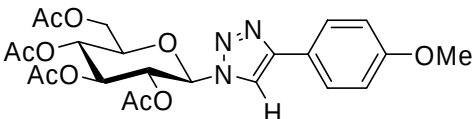
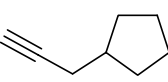
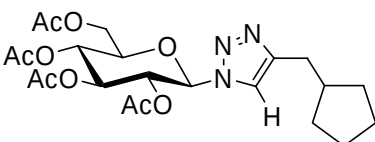
ACKNOWLEDGEMENTS

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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

^aSatisfactory ¹H NMR, ¹³C 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), CuSO₄ (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 °C 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 °C; [α]_D -85.8° (c 1.0, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 1.88, 2.03, 2.07, 2.08 (4 x s, 3H each, 4 x COCH₃), 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₂₂H₂₅N₃O₉ (+Na): 498.1488, found 498.1451.¹⁴
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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 chloride¹⁸ with propargyl alcohol in pyridine: mp 138-141 °C; [α]_D +10.8° (c 1.0, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 2.04, 2.05, 2.07, 2.13 (4 x s, 3H each, 4 x COCH₃), 2.53 (t, 1H, *J* = 2.5 Hz, alkyne-H), 4.24 (d, 1H, *J* = 9.5 Hz, H-5), 4.71 (m, 2H, CH₂), 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 $\text{C}_{17}\text{H}_{20}\text{O}_{11}$ (+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 °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 °C; $[\alpha]_{\text{D}} -5.8^\circ$ (c 1.2, CH_2Cl_2); ^1H 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*}, $-\text{OCH}_2$ -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 $\text{C}_{31}\text{H}_{39}\text{N}_3\text{O}_{20}$ (+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 °C; $[\alpha]_{\text{D}} -3.2^\circ$ (c 1.0, CH_2Cl_2); ^1H 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 $\text{C}_{15}\text{H}_{22}\text{O}_6$ (+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 °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 °C; $[\alpha]_{\text{D}} -44.3^\circ$ (c 1.1, CHCl_3); ^1H 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, $-\text{OCH}_2$ -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 C₂₉H₄₁N₃O₁₅ (+Na): 694.2435, found 694.2433.

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