‘Click’ Chemistry on Sugar-Derived Alkynes: A Tandem ‘Click–Click’ Approach to Bistriazoles

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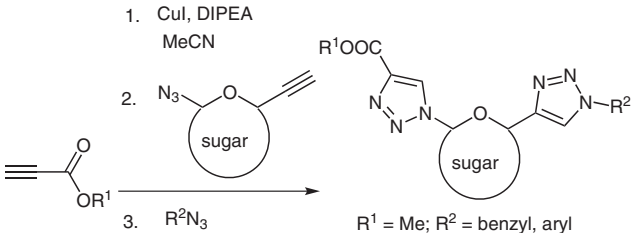
Abstract: Development of a tandem ‘click–click’ approach to the formation of successive 1,4-disubstituted 1,2,3-triazole linkages and ‘click chemistry’ on sugar-derived alkynes are described.

Key words: C-glycoside, triazole, ‘click’ reaction, alkyne, azide, azido-alkyne, bistriazole

The C-glycosides are an important class of glycosides with a sizeable number of natural products belonging to this category. They differ from the usual O-glycosides and N-glycosides in having a C–C bond attached to the anomeric carbon.[1] Due to this key change in the nature of this bond, C-glycosides appear to show significant resistance to hydrolytic and enzymatic cleavage and are generally considered as potential drug candidates. In view of the interesting behavior of C-glycosides, several synthetic approaches have been developed to synthesize a variety of C-glycosides and to study their properties.[2] Several C-glycosides have been synthesized and their utility as probes and inhibitors for biological processes have been studied.[1,3] Furthermore, the intriguing biological profiles of triazole-based molecules, such as their anti-HIV[4] and antimicrobial[5] activity, have drawn interest from various quarters in preparing a library of triazole-based C-glycosides. In the field of bioconjugation chemistry,[6] the biocompatible nature and the inertness of the triazole ring to metabolic transformations[7] has made it a good linker for joining two biomolecules in a covalent manner. This approach uses Cu(I)-catalyzed Hüisgen 1,3-dipolar cycloaddition[8] (‘click’) reactions, discovered independently by the groups of Sharpless and Meldal.[9]

In light of its salient features, such as selectivity and functional group tolerance, the emerging[10] ‘click’ reaction has found tremendous applications in the fields of drug discovery and material science, etc., in addition to bioconjugation.[6,11] For instance, in sugar chemistry, linking of a carbohydrate with another unit or with a non-carbohydrate system has been accomplished through a 1,2,3-triazole ring using the ‘click’ reaction of alkynes and azides.[12] Later, Dondoni and co-workers reported an iterative Cu(I)-catalyzed synthesis of triazole-linked oligomannoses from orthogonally protected mannose-derived alkynes and azides.[13] Also, there are a few reports on using iterative ‘click’ chemistry to generate triazole-linked oligomers, albeit not on carbohydrates.[14]



Scheme 1 Tandem click approach to the synthesis of bistriazoles

Nevertheless, there has been a quest to develop a one-pot approach to the successive linking of carbohydrates through triazole rings. There are a few reports in the literature where multiple triazole rings are formed in one pot by ‘click’ reactions between one component having one or more alkyne moieties with a second component having one or more azide moieties.[11,15] While Hotha et al. reported intramolecular ‘click’ reactions of azido-alkynes for the synthesis of triazole-fused tetracyclic compounds, Chandrasekhar et al. achieved the synthesis of furanotriazole macrocycles by inter and intramolecular ‘click’ reactions of azido-alkynes.[16]

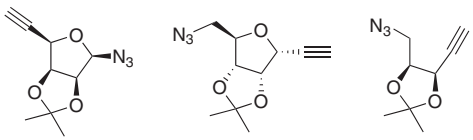


Figure 1 Designed azido-alkynes

However, there has been no report on the formation of multiple triazole rings in one pot by intermolecular ‘click’ reaction between an azido-alkyne, an alkyne and an azide. This stimulated us to develop a tandem ‘click’ approach especially for the synthesis of triazole-linked sugar oligomers. During the course of our investigation on this issue, Leigh and Aucagne reported a one-pot ‘click–click’ procedure for the successive copper- and copper-and-silver-mediated chemoselective formation of two distinct triazole linkages from amino acid derived alkynes and azides, using the trimethylsilyl group as a temporary masking group for one of the alkyne moieties.[17] This prompted us to disclose our initial results on developing a tandem ‘click’ approach to the formation triazole linkages succes-

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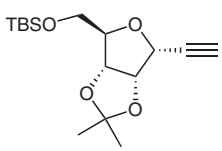
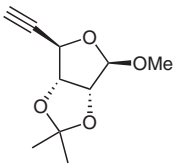
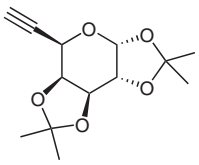
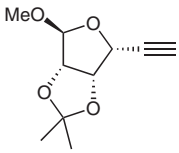
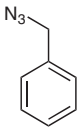
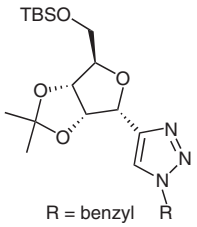
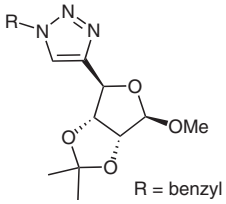
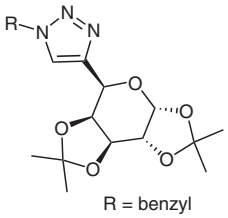
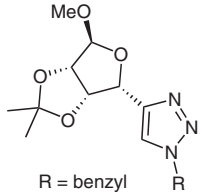
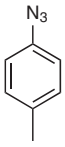
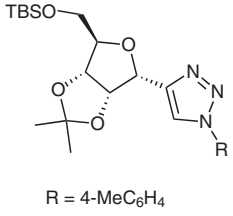
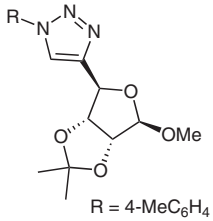
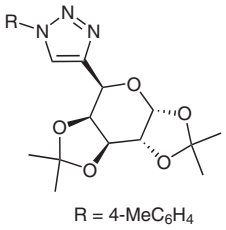
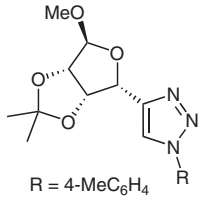
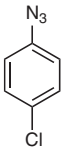
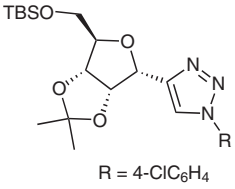
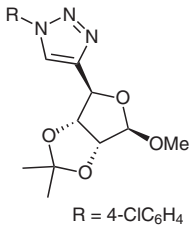
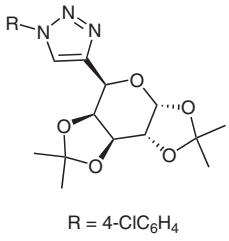
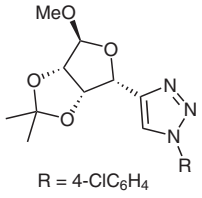
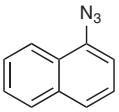
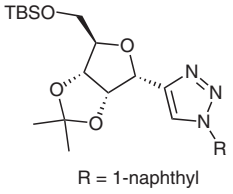
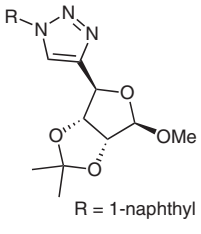
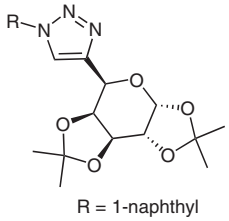
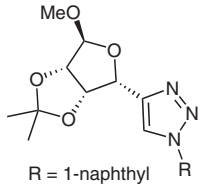
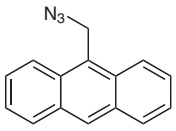
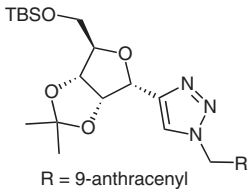
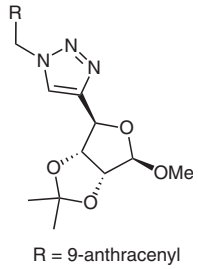
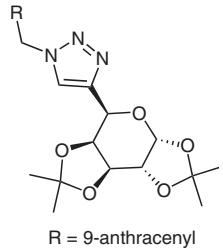
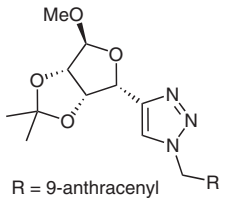
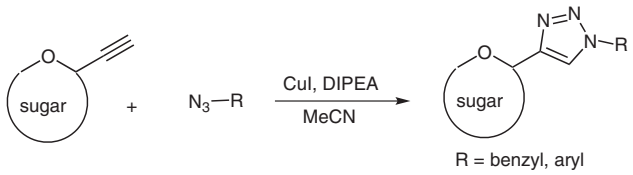
sively in one pot (Scheme 1) using sugar-derived azidoalkynes (Figure 1).

Before realizing this tandem 'click' chemistry, our initial task was to identify the best reaction conditions for this approach. To this end, we carried out 'click' reactions be-

Table 1 'Click' Chemistry between Sugar-Derived Alkynes and Azides[a]

Alkynes/azides	 **1**	 **2**	 **3**	 **4**
 **5**	 **10** (80)	 **11** (86)	 **12** (85)	 **13** (82)
 **6**	 **14** (81)	 **15** (83)	 **16** (84)	 **17** (82)
 **7**	 **18** (82)	 **19** (86)	 **20** (88)	 **21** (87)
 **8**	 **22** (75)	 **23** (85)	 **24** (86)	 **25** (83)
 **9**	 **26** (83)	 **27** (84)	 **28** (98)	 **29** (86)

[a] Yield given in parentheses.

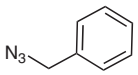
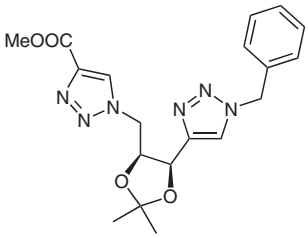
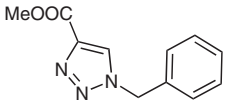
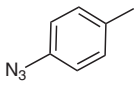
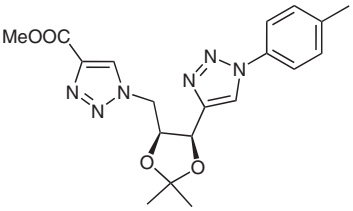
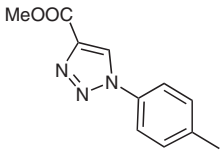
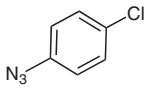
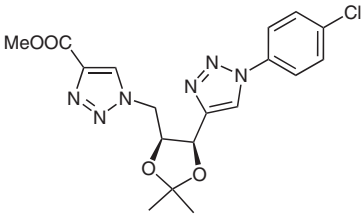
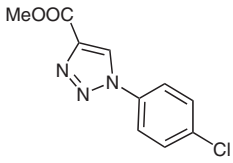
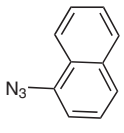
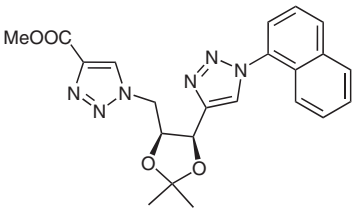
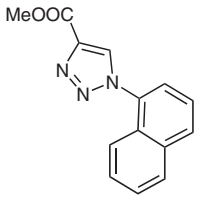
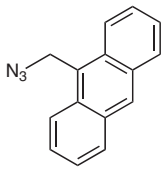
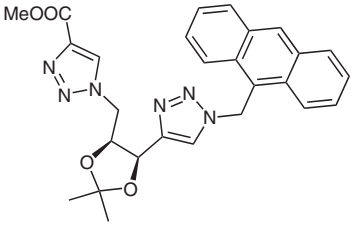
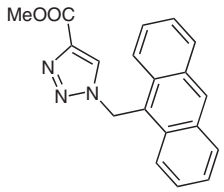


Scheme 2 'Click' reaction between sugar-derived alkynes and azides

tween simple sugar-derived alkynes and azides (Scheme 2). Although $CuSO_4$/sodium ascorbate-based 'click' protocol has proven to be the most benign, for our substrates, this method took a long time (more than 15 h) for the reaction to go to completion. This observation led us to follow another well-established 'click' protocol using copper(I) iodide, acetonitrile, and diisopropylethylamine (DIPEA).[9b] As expected, the copper(I)-catalyzed Hüisgen 1,3-dipolar cycloaddition reaction between known alkynes[18] and azides[19] proceeded smoothly to afford the corresponding 1,4-disubstituted 1,2,3-triazoles in excellent yield. The reaction went to completion within 15–20 min (Table 1).[20]

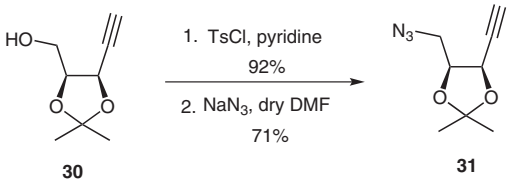
Having succeeded in synthesizing 1,2,3-triazoles derived from sugars, we turned to our main goal of devising a tandem 'click' approach using the same reaction conditions.

Table 2 Synthesis of Bistriazoles by a Tandem 'Click–Click' Approach Using Azido-alkyne **31**, Methyl Propiolate **32** and Azides **5–9**[a]

Azide	Product	By-product
 **5**	 **33** (23)	 **34** (33)
 **6**	 **35** (46)	 **36** (50)
 **7**	 **37** (38)	 **38** (36)
 **8**	 **39** (33)	 **40** (39)
 **9**	 **41** (45)	 **42** (48)

[a] Yield given in parentheses.

As shown in Scheme 1, we presumed that successive addition of CuI, DIPEA and an azido-alkyne to a solution of an alkyne in acetonitrile, would result in a 'click' reaction to form the first triazole linkage. Subsequent addition of a second azide to this reaction mixture would lead to the formation of the second triazole. This process could perhaps be repeated several times in order to access triazole oligomers in one pot by sequential addition of the azido-alkyne prior to the addition of the azide; the progress of the reaction could be monitored by thin layer chromatography from the consumption of the azido-alkyne at each stage of the sequence. We chose azido-alkyne **31** as our substrate for this sequence, which was easily prepared from the known alkynol[21] in two steps. Tosylation of primary alcohol **30** followed by an S_N2 displacement with sodium azide in *N*,*N*-dimethylformamide, afforded the azido-alkyne **31** in good yield (Scheme 3). Then, as shown in Scheme 1, copper(I) iodide and DIPEA were added to a solution of methyl propiolate **32** in acetonitrile. After stirring for a few minutes, the reaction mixture was treated with azido-alkyne **31** and the mixture was stirred for 15 minutes; the consumption of the azido-alkyne was monitored by thin layer chromatography. Addition of benzylazide **5** followed by stirring for another 15 minutes resulted in the formation of bistriazole **33** (23% yield), but along with the formation of the simple cycloadduct **34** (33%) as a by-product produced by a 'click' reaction between methyl propiolate and benzylazide. However, the yield of the desired reaction was improved to 46% by increasing the stirring time to one hour prior to the addition of the azide. In this case, the azido-alkyne was purified prior to use by rapid filtration through a short silica gel column.



Scheme 3 Synthesis of azido-alkyne **31**

The azido-alkyne **31** was found to decompose, both on storage and during the reaction, to give unidentified products. Consequently, the yield of the desired product became poor, leaving the other two partners to react and give the by-product **34**. Under the above reaction conditions, other bistriazoles **35**, **37**, **39** and **41** were also synthesized as shown in Table 2.[22]

In summary, we have explored the 'click' chemistry of sugar-derived alkynes and developed a tandem 'click–click' approach to the synthesis of 1,4-disubstituted 1,2,3-bistriazoles. Efforts are in progress to optimize the reaction conditions and improve the yield with different cyclic sugar-derived azido-alkynes (Figure 1) and also extend this strategy for the synthesis of triazole-linked sugar oligomers.

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(20) **Typical procedure for the simple 'click' reaction**: To a solution of alkyne **3** (0.050 g, 0.19 mmol) and azide **5** (0.026 g, 0.19 mmol) in MeCN (1.9 mL) were added CuI (0.0746 g, 0.38 mmol) and DIPEA (0.1 mL, 0.57 mmol) successively at r.t. After stirring for 30 min, the reaction was quenched by adding sat. aq NH_4Cl (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). After washing with brine (20 mL), the organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo to give the crude product, which was purified by recrystallisation from CH_2Cl_2–hexanes. The mother liquor was further purified by column chromatography (hexanes–EtOAc, 1.5:1) to afford triazole **12** (0.065 g, 85%). R_f = 0.62 (EtOAc–hexanes, 1:1); mp 155–157 °C; $[a]^{20}_D$ –83.880 (*c* 0.21, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (s, 1 H), 7.38–7.25 (m, 5 H), 5.59 (d, *J* = 11.6 Hz, 1 H), 5.57 (d, *J* = 1.2 Hz, 1 H), 5.43 (d, *J* = 14.8 Hz, 1 H), 5.18 (d, *J* = 2 Hz, 1 H), 4.70 (dd, *J* = 8.0, 2.4 Hz, 1 H), 4.36 (dd, *J* = 4.8, 2.4 Hz, 1 H), 1.59 (s, 3 H), 1.41 (s, 3 H), 1.35 (s, 3 H), 1.31 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.5, 134.5, 128.9, 128.5, 128.0, 123.0, 109.1, 108.9, 96.4, 72.5, 70.6, 70.5, 64.6, 54.0, 26.1, 25.8, 24.8, 24.1; IR (KBr): 3019, 2923, 2395, 1966, 1651, 1374, 1259, 1215, 1069 cm^{-1}; HRMS (EI): *m*/*z* calcd for $C_{20}H_{26}N_3O_3$: 388.1872; found: 388.1892.
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(22) **Typical procedure for the double 'click' reaction:** To methyl propiolate **32** (0.024 mL, 0.27 mmol) in MeCN (1.5 mL) was added CuI (0.105 g, 0.552 mmol) and DIPEA (0.147 mL, 0.82 mmol). The reaction mixture became a clear solution. The azido-alkyne **31** (0.050 g, 0.27 mmol) was added and the reaction was stirred for 1 h (reaction monitored by TLC). Then, azide **6** (0.27 mmol) was added and the reaction was stirred for 15 minutes. The reaction was quenched by the addition of sat. aq NH_4Cl (10 mL), the organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). After washing with brine (20 mL), the organic layer was dried over Na_2SO_4 and concentrated in vacuo to give the crude product, which was purified by recrystallization from CH_2Cl_2–hexanes. The mother liquor was purified by column chromatography (hexanes–EtOAc, 1:1.5) to afford triazole **35** (0.050 g, 46%). Compound **35**: R_f = 0.54 (EtOAc); mp 218–220 °C; $[a]^{20}_D$ –55.148 (*c* 0.38, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.32 (s, 1 H), 7.97 (s, 1 H), 7.59 (d, *J* = 8.5 Hz, 2 H), 7.33 (d, *J* = 8.1 Hz, 2 H), 4.95–4.64 (m, 4 H), 3.96 (s, 3 H), 2.43 (s, 3 H), 1.51 (s, 3 H), 1.39 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.8, 135.0, 130.2, 129.2, 129.1, 128.9, 128.2, 122.3, 109.3, 78.2, 72.1, 54.3, 52.2, 50.4, 26.7, 26.7, 21.1. IR (KBr): 3135, 3019, 2953, 2400, 1714, 1545, 1450, 1436, 1372, 1357, 1334, 1239, 1216, 1174, 1123, 1110, 1073, 1047 cm^{-1}; HRMS (EI): *m*/*z* calcd for $C_{19}H_{23}N_6O_4$: 399.5706; found: 399.5701. Compound **36**: R_f = 0.68 (EtOAc); mp 134–136 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.47 (s, 1 H), 7.63 (d, *J* = 8.5 Hz, 2 H), 7.35 (d, *J* = 8.1 Hz, 2 H), 3.99 (s, 3 H), 2.44 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.8, 135.0, 130.2, 121.5, 120.6, 109.3, 52.0, 21.1; IR (KBr): 3019, 2928, 2857, 1726, 1552, 1521, 1434, 1259, 1215, 1148, 1038 cm^{-1}; HRMS (EI): *m*/*z* calcd for $C_{11}H_{12}N_3O_2$: 218.0861; found: 218.0865.