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Cu(I)-Catalyzed cycloaddition of constrained azido-alkynes: access to 12- to 17-membered monomeric triazolophanes incorporating furanoside rings

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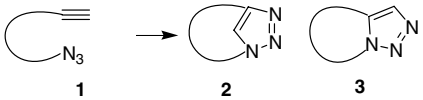
Abstract—A strained monomeric 12-membered triazolophane was formed by the Cu(I)-catalyzed intramolecular cycloaddition of an azide to an alkyne having a constrained tether incorporating an aromatic ring and a furanoside ring. Similar cycloadditions of azido-alkynes having ester, furanoside and peptidic tethers led to the formation of monomeric triazolophanes of higher ring sizes.

The azide–alkyne cycloaddition reaction is one of the best known of the 1,3-dipolar cycloadditions.[1] The importance of this reaction has been significantly augmented by the recent upsurge in its application in 'click' chemistry.[2] A remarkable development in the azide–alkyne cycloaddition was achieved via the introduction of methods for regioselective formation of 1,4-disubstituted-1,2,3-triazoles,[3] and 1,5-disubstituted-1,2,3-triazoles.[4] In particular, the generally efficient Cu(I)-catalyzed azide–alkyne cycloaddition affording 1,4-disubstituted-1,2,3-triazoles as the exclusive products has made this cycloaddition an invaluable tool in click chemistry,[2] and is currently being applied in the 'ligation' of two different molecules of chemical and biochemical relevance.[5] Intramolecular uncatalyzed cycloaddition of an azido-alkyne resulting in five- to seven-membered rings fused to a triazole ring is a well-known process.[6] Cyclodimerization of peptides and glycopeptides involving Cu(I)-catalyzed azide–alkyne cycloadditions leading to relatively strain-free rings has been reported.[5g,k–n] However, monocyclization of azido-alkynes resulting in strained ring systems using this cycloaddition remained unknown, and only very recently Burgess et al. reported the synthesis of some 14-membered monomeric cyclic peptides incorporating 1,4-disubstituted triazole rings.[5o] This work has prompted us to describe herein our synthesis of 12- to 17-membered triazolophanes by Cu(I)-catalyzed azide–alkyne cycloaddition.

A suitably sized azido-alkynes **1** can lead to the bicyclic triazoles **2** or **3** or both depending on the regioselectivity of the reaction (Scheme 1). The 1,4-disubstituted triazole **2** is particularly interesting, because relatively small-sized rings having this structural type would represent strained triazolophanes. We envisaged that the use of aromatic rings, furanoside rings and peptides as constraints incorporated in the tethered azido-alkynes would facilitate their monocyclization leading to the aforementioned triazolophanes. The azido-alkyne **9** having a nine-atom tether incorporating two aromatic rings was prepared from salicylaldehyde **4** and the bromo compound **6** according to Scheme 2. Other furanoside- and peptide-appended azido-alkynes were prepared according to Scheme 3. Results of the cycloaddition of these substrates are presented in Table 1.



Scheme 1. Intramolecular azide–alkyne cycloaddition.

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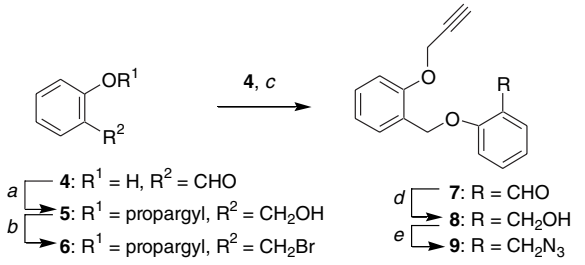
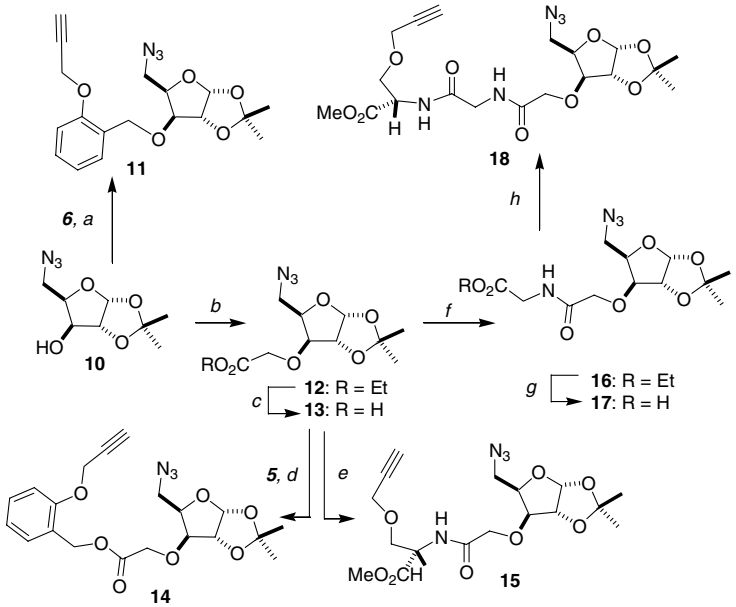


Scheme 2. Synthesis of azido-alkyne **9**. Reagents and conditions. (a) (i) Bu_4NBr, 50% aq NaOH, propargyl bromide, CH_2Cl_2, 12 h, 77%; (ii) $NaBH_4$, MeOH, 25 °C, 6 h, 95%. (b) PBr_3, Et_2O, 25 °C, 2 h, 91%. (c) K_2CO_3, DMF, 80–100 °C, 12 h, 85%. (d) $NaBH_4$, MeOH, 25 °C, 6 h, 93%. (e) (i) PBr_3, Et_2O, 25 °C, 2 h; (ii) NaN_3, DMF, 60 °C, 24 h, 91%.

Treatment of a freshly prepared sample of **9** with 1.0 mol % of $CuSO_4$ and 10 mol % sodium ascorbate in *t*-butanol–water (1:1) at 25 °C for 15 h gave a complex mixture of products, from which was isolated in 31% yield a triazole having a molecular weight of 293 (positive ion ESI and EI) consistent with the monomeric triazole structure **19** or its 1,4-regioisomer.[7] No dimeric product could be isolated from the reaction. Although the NOESY spectrum of the compound hinted at the 1,5-substituted structure **19**, confirmation of the structure came from X-ray diffraction analysis of the product (Fig. 1).[8] The result was rather surprising as 1,4-regioselectivity in Cu(I)-catalyzed azide–alkyne cycloadditions has been observed in all such reported reactions until now. The triazole **19** was not formed when **9** was subjected to the reaction conditions without the addition of the copper salt and sodium ascorbate the starting material **9** being recovered unchanged. So it was evident that Cu(I) did catalyze the reaction, but led to 1,5-regioselectivity. Although the reasons for this result are not known, it is probable that the presence of the constrained tether in **9** facilitated cycloaddition to the 11-membered triazolophane **19**. The corresponding 1,4-disubstituted compound would be more strained and consequently was not formed. The same product was obtained in 22% yield under thermal cycloaddition conditions involving refluxing in toluene for 6 h.

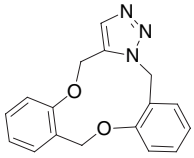
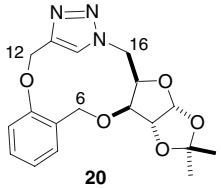
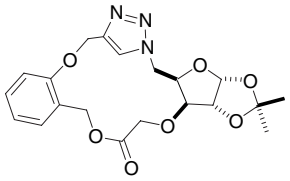
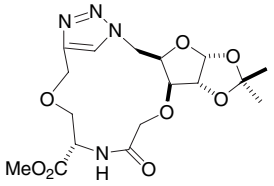
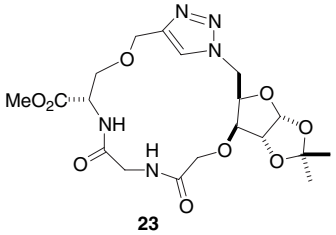
The well-known 1,2-isopropylidenefuranose skeleton has been previously used as a scaffold for carrying out intramolecular nitrile oxide cycloaddition for the synthesis of 10- to 12-membered ring compounds.[9] The Cu(I)-catalyzed cycloaddition of **11**, which differs from **9** by having a furanoside ring instead of an aromatic ring as a constraint, led to the formation of a monomeric triazole in 35% yield as evidenced by ^1H and ^{13}C NMR and mass spectroscopic analysis. The liquid nature of this product precluded X-ray diffraction analysis. The NOESY spectrum indicated an NOE between the triazole proton and 12-H as well as between the triazole proton and 16-H/6-H.[10] These NOE characteristics led to the assignment of structure **20** to this product. To our knowledge, **20** represents the first example of a 12-membered triazolophane. The Cu(I)-catalyzed cycloaddition of the ester-linked azido-alkyne **14** and the furanoside-peptidic azido-alkynes **15** and **18**, all having longer tethers than **11**, furnished the monomeric triazoles—15-membered **21** (32%), 14-membered **22** (32%) and 17-membered **23** (31%), respectively, as the exclusive products of cycloaddition (Table 1).

The establishment of the monomeric nature of the triazolophanes **19**–**23** was based mainly on their mass spectroscopic molecular weights. The positive ion ESI mass spectra of these compounds were checked carefully in order to ascertain that the peaks were due to $(M+Na)^+$ and not to doubly charged species of the type $(2M+2Na)^{2+}$. Formation of dimeric products was not



Scheme 3. Synthesis of azido-alkyne intermediates. Reagents and conditions. (a) NaH, THF, 25 °C, 12 h, 71%; (b) NaH, THF, $BrCH_2CO_2Et$, 25 °C, 12 h, 86%; (c) LiOH, MeOH, 25 °C, 6 h, 92%; (d) EDCI, DMAP, CH_2Cl_2, 25 °C, 12 h, 77%; (e) *O*-propargylserine methyl ester, EDCI, CH_2Cl_2, 25 °C, 12 h, 53%; (f) glycine ethyl ester hydrochloride, EDCI, Et_3N, CH_2Cl_2, 25 °C, 12 h, 77%; (g) LiOH, MeOH, 25 °C, 6 h, 87%; (h) *O*-propargylserine methyl ester, EDCI, CH_2Cl_2, 25 °C, 12 h, 54%.

Table 1. Monomeric triazolophanes from furanoside-tethered azido-alkynes via Cu(I)-catalyzed intramolecular azide–alkyne cycloaddition[a]

Entry	Azido-alkyne	Product	Yield (%)[b] [%][c]
1	**9**	 **19**	[31]
2	**11**	 **20**	[35]
3	**14**	 **21**	[32]
4	**15**	 **22**	(22) [32]
5	**18**	 **23**	(20) [31]

[a] Azide–alkyne cycloaddition was performed under either one or both of the following conditions. [A] Stirring a mixture of the azido-alkyne in THF in the presence of CuI (1.1 equiv) and DIPEA (25 equiv) at 25 °C for 24 h. [B] Stirring a mixture of the azido-alkyne in *t*-BuOH–H_2O in the presence of $CuSO_4 \cdot 5H_2O$ (1 mol %) and sodium ascorbate (10 mol %) at 25 °C for 12–24 h.

[b] Chromatographically isolated yields under conditions [A].

[c] Chromatographically isolated yields under conditions [B].

observed in these reactions, although in some cases compounds were isolated, the mass, IR and ^1H NMR spectra of which indicated them to be azido-alkynes derived from the intermolecular cycloaddition of two azido-alkyne molecules.

In contrast to the high yields generally reported for Cu(I)-catalyzed azide–alkyne cycloadditions, yields of the aforementioned cycloaddition reactions were found to be low, and could not be improved by changing solvents or using larger quantities of the copper salts.

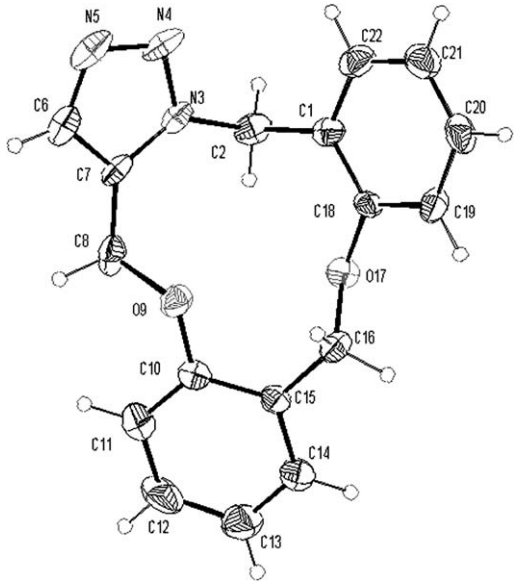


Figure 1. ORTEP view of **19** showing the atom numbering scheme (ellipsoids drawn at 30% probabilities).

Cycloaddition in the presence of CuI and di-*i*-propylethylamine led to poorer yields (Table 1). Attempted cycloaddition of **9** in a micellar environment containing SDS and copper salts was unsuccessful leading to the recovery of the starting material. It is possible that polymerization of the alkynes in the presence of copper salts resulted in the formation of intractable products leading to poor yields of the reactions. Despite the poor yields, the aforementioned cycloaddition provided an access to strained rings.

In conclusion, the above work has revealed an interesting and useful aspect of the click azide–alkyne cycloaddition whereby strained monomeric triazoles including triazolophanes were synthesized from azido-alkynes having tethers incorporating aromatic, furanoside and peptidic moieties. The presence of the furanoside ring and different peptidic tethers in the azido-alkynes make this cycloaddition strategy potentially important for the synthesis of peptidomimetics as well as novel nucleoside derivatives.

Acknowledgements

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7. Spectral and other physical data of the triazoles—Compound **19**: white solid, mp 233–235 °C, IR (KBr): 2933, 1603 cm^{-1}; MS (EI): *m*/*z* 293 (M); ^1H NMR (300 MHz, $CDCl_3$): δ 7.92 (d, $J = 7.5$ Hz, 1H), 7.71 (s, 1H), 7.44–7.30 (m, 3H), 7.13–7.03 (m, 4H), 5.58 (s, 2H), 5.21 (s, 2H), 5.08 (s, 2H), 2.17 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.9 (q), 157.4 (q), 136.6 (CH), 133.9 (CH), 132.3 (CH), 131.8 (q), 130.6 (CH), 130.4 (CH), 130.2 (CH), 126.6 (q), 124.9 (q), 122.5 (CH), 116.1 (CH), 115.1 (CH), 71.6 (CH_2), 60.6 (CH_2), 45.5 (CH_2) Calcd. for $C_{17}H_{15}N_3O_2$, C, 69.61; H, 5.15; N, 14.33. Found, C, 69.32; H, 5.29; N, 14.17. Compound **20**: colourless liquid; $[\alpha]_D^{25}$ −80.8 (*c* 0.32, $CHCl_3$); IR (Neat): 2980, 2927 cm^{-1}; MS (ESI): *m*/*z* 360 (M+H), 382 (M+Na); ^1H NMR (300 MHz, $CDCl_3$): δ 7.76 (s, 1H), 7.35 (t, $J = 7.6$ Hz, 1H), 7.19 (d, $J = 7.3$ Hz, 1H), 7.06–6.98 (m, 2H), 5.93 (d, $J = 3.5$ Hz, 1H), 5.46 (d, $J = 12.0$ Hz, 1H), 4.94 (dt, $J = 10.3$, 2.6 Hz, 1H), 4.84 (d, $J = 11.9$ Hz, 1H), 4.76–4.68 (m, 3H), 4.52 (dd, $J = 12.7$, 2.6 Hz, 1H), 4.43 (d, $J = 10.6$ Hz, 1H), 3.71 (d, $J = 2.5$ Hz, 1H), 1.53 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.4 (q), 134.3 (CH), 132.8 (q), 130.5 (CH), 130.1 (CH), 126.9 (q), 122.3 (CH), 114.6 (CH), 112.4 (q), 104.9 (CH), 81.8 (CH), 80.9 (CH), 79.3 (CH), 70.9 (CH_2), 59.2 (CH_2), 44.2 (CH_2), 26.8 (CH_3), 26.3 (CH_3) Calcd. for $C_{18}N_{21}N_3O_5$, C, 60.16; H, 5.89; N, 11.69. Found, C, 59.87; H, 6.01; N, 11.45. Compound **21**: white foam; $[\alpha]_D^{25}$ −81.1 (*c* 1.10, $CHCl_3$); IR (KBr): 3169, 1749 cm^{-1}; MS (ESI): *m*/*z* 418 (M+H), 440 (M+Na); ^1H NMR (300 MHz, $CDCl_3$): δ 7.90 (s, 1H), 7.38 (t, $J = 7.6$ Hz, 1H), 7.29 (d, $J = 8.1$ Hz, 1H), 7.09 (d, $J = 8.2$ Hz, 1H), 6.98 (t, $J = 7.4$ Hz, 1H), 5.95 (d, $J = 3.7$ Hz, 1H), 5.83 (d, $J = 11.5$ Hz, 1H), 5.42 (d, $J = 12.6$ Hz, 1H), 5.29 (d, $J = 12.4$ Hz, 1H), 4.85 (d, $J = 11.6$ Hz, 1H), 4.81–4.76 (m, 2H), 4.58 (d, $J = 11.0$ Hz, 1H), 4.53 (d, $J = 11.6$ Hz, 1H), 4.30 (d, $J = 15.5$ Hz, 1H), 3.63 (d, $J = 15.5$ Hz, 1H),3.52 (d, $J = 3.1$ Hz, 1H), 1.47 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.0 (q), 157.1 (q), 144.1(q), 131.7 (CH), 131.0 (CH), 125.5 (CH), 124.4 (q), 121.6 (CH), 113.6 (CH), 112.3 (q), 105.1 (CH), 82.5 (CH), 81.1 (CH), 77.8 (CH), 67.5 (CH_2), 63.6 (CH_2), 63.0 (CH_2), 47.2 (CH_2), 27.2 (CH_3), 26.6 (CH_3) Calcd. for $C_{20}H_{23}N_3O_7$, C, 57.55; H, 5.55; N, 10.07. Found, C, 57.39; H, 5.33; N, 10.29. Compound **22**: colourless liquid; $[\alpha]_D^{25}$ −63.6 (*c* 1.01, $CHCl_3$); IR (KBr): 3411, 3275, 1744, 1676 cm^{-1}; MS (ESI): *m*/*z* 413 (M+H), 435 (M+Na), 451 (M+K); ^1H NMR (300 MHz, $CDCl_3$): δ 7.97 (s, 1H), 6.00 (d, $J = 3.7$ Hz, 1H), 5.35 (broad multiplet, 1H), 5.03 (dd, $J = 15.0$, 2.4 Hz, 1H), 4.79 (dd, $J = 15.0$, 5.0 Hz, 1H), 4.65 (s, 2H), 4.59 (d, $J = 3.7$ Hz, 1H), 4.22–4.11 (m, 3H), 4.04–3.94 (m, 3H), 3.84–3.78 (m, 1H), 3.72 (s, 3H), 1.54 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.0 (q), 167.5 (q), 144.7 (q), 125.2 (CH), 112.3 (q), 104.3 (CH), 83.6 (CH), 80.9 (CH), 75.9 (CH), 68.6 (CH_2), 67.8 (CH_2), 63.9 (CH_2), 53.8 (CH), 52.6 (CH_3), 48.2 (CH_2), 26.6 (CH_3), 26.0 (CH_3). Compound **23**: Yield: white foam; $[\alpha]_D^{25}$ −21.4 (*c* 1.10, $CHCl_3$); IR (Neat) : 3338, 1744, 1672 cm^{-1}; MS (ESI): *m*/*z* 470 (M+H), 492 (M+Na); ^1H NMR (300 MHz, $CDCl_3$): δ 7.78 (s, 1H), 7.23 (br s, 1H), 6.85 (d, $J = 7.1$ Hz, 1H), 5.97 (d, $J = 3.5$ Hz, 1H), 4.87–4.49 (m, 7H), 4.32–4.04 (m, 4H), 3.95–3.72 (m, 6H), 1.51 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9 (q), 169.3 (q), 168.8 (q), 146.2 (q), 123.8 (q), 112.4 (q), 104.8 (CH), 82.8 (CH), 81.4 (CH), 77.4 (CH), 70.1 (CH_2), 68.4 (CH_2), 65.3 (CH_2), 53.2 (CH_3), 52.8 (CH), 46.9 (CH_2), 43.1 (CH_2), 26.7 (CH_3), 26.2 (CH_3) Calcd. for $C_{19}H_{27}N_5O_9$, C, 48.61; H, 5.80; N, 14.92. Found, C, 48.37; H, 5.62; N, 14.71.
8. Crystal data for **19**: $C_{17}H_{15}N_3O_2$, $M = 293.32$, crystal dimensions $0.39 \times 0.10 \times 0.08$ mm, monoclinic space group $P2_1/c$, $a = 4.210(2)$, $b = 11.447(6)$, $c = 29.611(16)$ Å, $\beta = 90.675(11)°$, $V = 1427.1(14)$ $Å^3$, $Z = 4$, $\rho_{calcd} = 1.365$ g cm^{-3}, μ (Mo-K_α) = 0.092 mm^{-1}, $F(000) = 616$, $2\theta_{max} = 50.00°$, 6938 reflections collected, 2486 unique, 1681 observed ($I > 2\sigma(I)$) reflections, 199 refined parameters, *R* value 0.1228, $wR2 = 0.2144$ (all data $R = 0.1801$, $wR2 = 0.2348$), $S = 1.265$, minimum and maximum transmission 0.9650 and 0.9930, respectively, maximum and minimum residual electron densities +0.241 and −0.188 e$Å^{-3}$, respectively.
   X-ray intensity data of **19** was collected on a Bruker SMART APEX CCD diffractometer with omega and phi scan mode, $\lambda_{MoK\alpha} = 0.71073$ Å at $T = 297(2)$ K. All the data were corrected for Lorentzian, polarization and absorption effects using Bruker's SAINT and SADABS programs. The crystal structure was solved by direct method using SHELX-97 and the refinement was performed by full matrix least squares of F^2 using SHELXL-97 (Sheldrick, G. M. SHELX-97 program for crystal structure solution and refinement, University of Göttingen, Germany, 1997). Hydrogen atoms were included in the refinement as per the riding model. Crystallographic data for **19** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 297356.
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10. The ^1H NMR spectrum (500 or 600 MHz) of **20** exhibited the crucial 16-H and 6-H protons as overlapping signals with little difference in chemical shifts. The observed NOE of the triazole proton with any one or both of these protons can only be explained by the structure **20**. In the alternative 1,5-substituted isomer these protons would be far apart, and no NOE would be expected.