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Expedient synthesis of 1,2,3-triazole-fused tetracyclic compounds by intramolecular Huisgen ('click') reactions on carbohydrate-derived azido-alkynes

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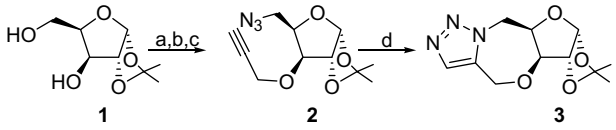
Abstract—An efficient, practical and convenient synthesis of 1,2,3-triazole-fused tetracyclic compounds was achieved by intramolecular 1,3-dipolar cycloaddition of carbohydrate-derived azido-alkynes.

Several compounds of the 1,2,3-triazole class possess a broad spectrum of biological properties including anti-HIV,[1a] anti-allergic,[1b] anti-bacterial,[1c] herbicidal and fungicidal activity.[1d] 1,2,3-Triazoles are synthesized by 1,3-dipolar cycloaddition of the corresponding azide and alkyne, a procedure known as the Huisgen reaction.[2] Furthermore, 1,2,3-triazole formation is a highly efficient reaction without any significant side products and is currently referred to as a 'click reaction'.[3] The significant biological profiles of 1,2,3-triazoles coupled with our interest in synthesizing chiral, oxygen-rich chemical libraries prompted us to develop a synthetic protocol that would enable the synthesis of a chiral, fused, polycyclic 1,2,3-triazole class of compounds. Towards this end, we considered performing the 1,3-dipolar cycloaddition reactions on carbohydrate-derived azido-alkynes in an intramolecular fashion. In this letter, we reveal an effective integration of click chemistry onto carbohydrate substrates in order to synthesize 1,2,3-triazole-fused tetracyclic compounds in high yields.

Carbohydrate-derived azido substrates for intramolecular click reactions were synthesized by an S_N2 displacement of the corresponding tosylates with NaN_3 (Scheme 1). Accordingly, xylofuranosyl diol **1**[4] was treated with



Scheme 1. Reagents and conditions: (a) *p*-TsCl, py., 0 °C–rt, 10 h, 91%; (b) NaN_3, DMF, 90 °C, 8 h, 95%; (c) NaH, propargyl bromide, DMF, 0 °C–rt, 2 h, 93%; (d) toluene, 100 °C, 2 h, 95%.

p-TsCl in the presence of pyridine for 10 h at 0 °C followed by treatment with sodium azide at 90 °C in DMF to afford the required 5-deoxyazidoxylofuranoside in 86% overall yield. The remaining hydroxyl group was converted into a propargyl ether using sodium hydride and propargyl bromide to afford the required azido-alkyne **2**.

In the ^{1}H NMR spectrum of the azido-alkyne **2**, resonances corresponding to the alkyne C*H* were identified at δ 2.48 (t, J = 2.3 Hz) ppm and the C-5 methylene protons as a multiplet at δ 3.51 ppm. The 1,3-dipolar cycloaddition reaction was carried out under reagent-free conditions by heating a toluene solution of the azido-alkyne **2** at 100 °C for 2 h.[5] The resultant tetracyclic 1,2,3-triazole **3** precipitated as a white solid on cooling to room temperature.

The ^{1}H NMR spectrum of **3** revealed an olefinic proton at δ 7.49 ppm as a singlet and the anomeric proton at δ 5.77 (d, J = 3.9 Hz) ppm; the high resolution NMR spectrum proved that the 1,3-dipolar cycloaddition had occurred in a regioselective manner. In the

Keywords: Click chemistry; Cycloaddition; Huisgen reaction; Carbohydrates; Diversity oriented synthesis.
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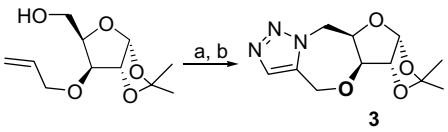


Scheme 2. Reagents and conditions: (a) MsCl, Et_3N, CH_2Cl_2, rt, 2.5 h; (b) NaN_3, DMF, 90 °C, 6 h, N_2.

^{13}C NMR spectrum, resonances characteristic of two olefinic carbons were present at δ 134.8 and 132.1 ppm with the rest of the spectrum in complete agreement with the assigned structure. During our studies, the formation of compound **3** was reported by Tripathi et al. starting from 1,2-*O*-isopropylidene 3-*O*-allyl glucofuranose (Scheme 2).[6]

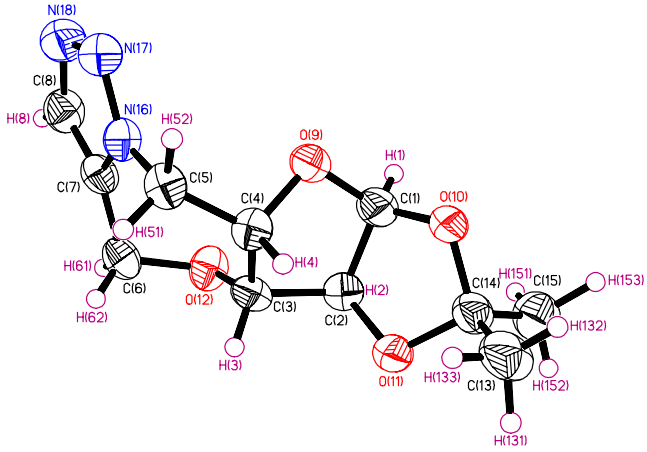
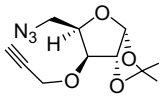
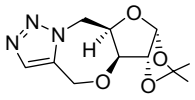
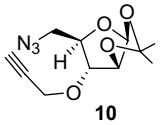
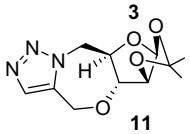
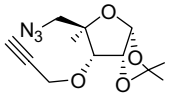
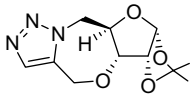
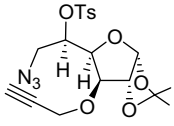
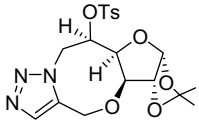
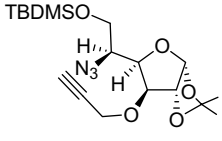
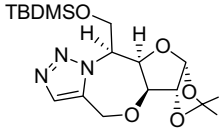
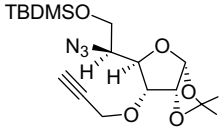
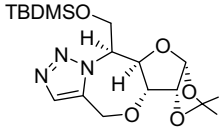
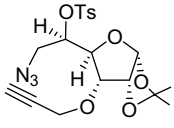
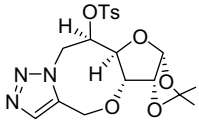
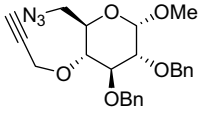
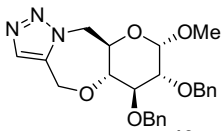
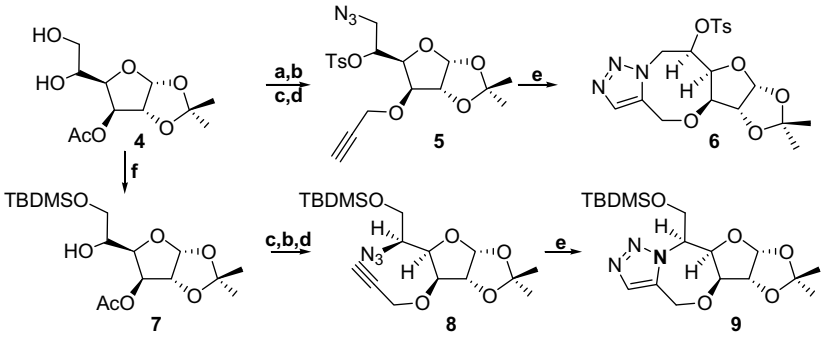


Figure 1. ORTEP diagram of compound **3**.

Table 1.

S. No.	Substrate	Product	Time (h)	Yield (%)
1	 **2**	 **3**	2	95
2	 **10**	 **11**	3.5	92
3	 **12**	 **13**	2	90
4	 **5**	 **6**	6	80
5	 **8**	 **9**	5	78
6	 **14**	 **15**	5	75
7	 **16**	 **17**	6.5	87
8	 **18**	 **19**	6	91



Scheme 3. Reagents and conditions: (a) *p*-TsCl, py., 0 °C–rt, 15 h, 86%; (b) NaN_3, DMF, 120 °C, 8 h, 92%; (c) *p*-TsCl, py., 100 °C, 6 h, 75%; (d) (i) NaOMe, MeOH, rt, 0.5 h, 96%; (ii) NaH, propargyl Br, DMF, 0 °C–rt, 2 h, 87%; (e) $C_6H_5CH_3$, 100 °C, 6 h; (f) TBDMSCl, im., DMF, 1 h, 84%.

This interesting observation was rationalized by assuming that the initial triazoline possibly had the trans ring fusion and was therefore oxidized by atmospheric oxygen. However, the spectral data of triazole **3** derived from propargyl ether **2** did not correlate with Tripathi et al. data.[6]

Compound **3** was crystallized by slow evaporation from light petroleum (60–80 °C) and dichloromethane, and was subjected to X-ray structure determination. Gratifyingly, the crystallographic analysis proved the structural authenticity of the tetracyclic triazole **3** beyond any doubt (Fig. 1).[6,7] The bond lengths between C7,C8 and N17,N18 were found to be 1.363 and 1.324 Å, respectively, confirming the presence of double bonds in the fused 1,2,3-triazole moiety.[7] It is interesting to note that the same set of reactions carried out on *arabino*- and *ribo*-derived azido-alkynes **10** and **12** also resulted in the formation of 1,2,3-triazole-fused tetracyclic compounds **11** and **13**. In addition, the versatility of the current protocol was demonstrated using a range of substrates comprising *gluco*-, *allo*-, *xylo*-, *ribo*- and *arabino*- derived azido-alkynes as depicted in Table 1.

We next synthesized 1,2,3-triazoles fused to hexofuranosyl-derived seven- and eight-membered rings (Scheme 3). Accordingly, the 3-*O*-acetyl derivative **4** was converted into the azido-alkyne **5** in four steps. The primary alcohol of compound **4**[8] was converted into the corresponding toluene *p*-sulfonate using *p*-TsCl, reacted with NaN_3 at 120 °C for 8 h and treated with *p*-TsCl to obtain an azido-tosylate that was subsequently converted to the required azido-alkyne **5**. The 'click' reaction was effected by heating a toluene solution of azido-alkyne **5** to 100 °C in toluene for 6 h to yield the triazole-fused tetracyclic compound **6**.[7,9] In another set of reactions, the primary hydroxyl group was protected as its *tert*-butyldimethylsilyl ether and the secondary hydroxyl group was converted to the azido-alkyne **8** using the aforementioned reagents and the click reaction was carried out to provide the triazole **9**.[9,10]

These reactions were performed on the *allo*-series **14** and **16** to obtain triazoles **15** and **17**. The glucopyranosylazido-alkyne **18** was also converted into the corresponding tricyclic compound **19** successfully.[9] In all cases, the formation of 1,2,3-triazole-fused tetracyclic compounds was found to be high yielding and in most of the substrates the resulting product precipitated from the reaction mixture.[9] Products were isolated either by filtration from the reaction mixture for solids (**3**, **6**, **11**, **13**, **17** and **19**) or by conventional silica gel column chromatography for gummy products (**9** and **15**).[5,9]

In conclusion, we have investigated 'click' chemistry using carbohydrates in an intramolecular fashion under reagent-free conditions. Our further efforts will be dedicated towards understanding biological profiles and developing a diversity oriented synthetic pathway. The results from these endeavours will be disclosed in the future.

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Supplementary data

Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2005.05.012.

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4. Hasegawa, A.; Kisho, M. *Carbohydr. Res.* **1980**, *79*, 265–270.
5. General experimental protocol: A solution of azido-alkyne **2** (250 mg, 0.9 mmol) in 2 mL of toluene was heated to 100 °C for the appropriate time and cooled to room temperature. The separated solid was filtered off and crystallized by slow evaporation using petroleum ether (60–80 °C) and CH_2Cl_2. In the cases of products **9** and **15** which did not result in a solid, the reaction mixture was concentrated in vacuo to give a crude residue, which was purified by passing through a pad of silica gel.
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7. Crystal data: $C_{11}H_{15}N_3O_4$, $M = 253.26$, orthorhombic, space group $P2_12_12_1$, $a = 5.495(1)$, $b = 10.054(2)$, $c = 21.330(4)$ Å, $V = 1178.4(4)$ Å^3, $Z = 4$, $D_{calcd} = 1.428$ g cm^{-1}, $T = 298(2)$ K, $\mu = 0.110$ mm^{-1}, $F(000) = 536$, λ = Mo Kα = 0.7107 Å, 5138 reflections measured, 1686 unique, observed with $I > 2\sigma(I)$, final $R_1 = 0.0283$, $wR_2 = 0.0306$. Crystallographic data has been deposited for compound **3** with the Cambridge Crystallographic Data Centre, [CCDC 264130]. Copies of the data can be obtained free of charge via ww.ccdc.cam.ac.uk/conts/retrieving.html or CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk).
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9. See Supplementary data.
10. Compound characterization data for:
Compound **3**: ^{1}H NMR [$CDCl_3$, 200 MHz]: δ 1.27, 1.46 (2s, 6H), 4.22 (d, 1H, $J = 2.1$ Hz), 4.39 (m, 1H), 4.49 (d, 1H, $J = 3.6$ Hz), 4.58 (d, 1H, $J = 14.7$ Hz), 4.69 (dd, 1H, $J = 15.2$, 2.4 Hz), 4.92 (d, 1H, $J = 14.7$), 5.11 (dd, 1H, $J = 5.6$, 15.5 Hz), 5.77 (d, 1H, $J = 3.6$ Hz), 7.49 (s, 1 H); ^{13}C NMR [$CDCl_3$, 50 MHz]: δ 26.0, 26.6, 48.00, 60.6, 74.2, 83.8, 84.4, 104.7, 111.9, 132.1, 134.8; IR (cm^{-1}): 1461, 1379; mp 200 °C. CHNS Anal. Calcd for $C_{11}H_{15}N_3O_4$ as C, 52.17%; H, 5.97%; N, 16.59%. Found: C, 51.97%; H, 5.46%; N, 16.67%.
Compound **6**: ^{1}H NMR [$CDCl_3$, 300 MHz]: δ 1.29, 1.48 (2s, 6H), 2.47 (s, 3H), 4.00 (m, 1H), 4.18 (m, 1H), 4.26 (dd, 1H, $J = 2.9$, 8.2 Hz), 4.54 (d, 1H, $J = 14.7$ Hz), 4.62 (d, 1H, $J = 3.6$ Hz), 4.67 (dd, 1H, $J = 3.2$, 12.4 Hz), 4.86 (d, 1H, $J = 14.7$ Hz), 5.11 (d, 1H, $J = 3.0$ Hz), 5.91 (d, 1H, $J = 3.8$ Hz), 7.39 (d, 2H, $J = 8.0$ Hz), 7.53 (s, 1H), 7.82 (d, 2H, $J = 8.0$ Hz); ^{13}C NMR [$CDCl_3$, 50 MHz]: 21.7, 26.1, 26.5, 48.2, 61.7, 69.8, 78.9, 81.3, 82.8, 104.9, 112.8, 127.8, 130.1, 133.1, 145.6; IR (cm^{-1}): 1726, 1597, 1454, 1377; mp 149 °C. CHNS Anal. Calcd for $C_{19}H_{23}N_3O_7S$ as C, 52.16%; H, 5.30%; N, 9.61%; S, 7.33%. Found: C, 51.20%; H, 4.97%; N, 9.65%; S, 7.06%.
Compound **9**: ^{1}H NMR [$CDCl_3$, 200 MHz]: δ 0.08, 0.13 (2s, 6H), 0.91 (s, 9H), 1.29, 1.48 (2s, 6H), 4.31 (d, 1H, $J = 2.1$ Hz), 4.39–4.65 (m, 4H), 4.70–4.95 (m, 3H), 5.72 (d, 1H, $J = 3.6$ Hz), 7.61 (s, 1 H); ^{13}C NMR [$CDCl_3$, 75 MHz]: δ 5.4, 5.6, 18.2, 20.6, 25.6, 25.8, 26.0, 26.6, 59.2, 60.0, 72.6, 83.7, 85.0, 104.3, 111.8, 131.9, 135.1; IR (cm^{-1}): 1722, 1462, 1375. CHNS Anal. Calcd for $C_{18}H_{31}N_3O_5Si$ as C, 54.38%; H, 7.86%; N, 10.57%. Found: C, 54.16%; H, 7.48%; N, 10.33%.
Compound **11**: ^{1}H NMR [$CDCl_3$, 300 MHz]: δ 1.43, 1.60 (2s, 6H), 3.56 (ddd, 1H, $J = 10.8$, 9.0, 2.9 Hz), 3.95 (dd, 1H, $J = 9.0$, 4.4 Hz), 4.36 (dd, 1H, $J = 13.2$, 10.8 Hz), 4.51 (d, 1H, $J = 14.9$ Hz), 4.73 (t, 1H, $J = 4.7$ Hz), 5.08 (d, 1H, $J = 14.9$ Hz), 5.31 (dd, 1H, $J = 13.4$,2.9 Hz), 5.75 (d, 1H, $J = 4.9$ Hz), 7.56 (s, 1H); ^{13}C NMR [$CDCl_3$, 50 MHz]: δ 27.8, 28.1, 52.3, 62.8, 74.6, 85.5, 93.2, 103.6, 115.79, 133.5, 136.2; IR (cm^{-1}): 1521, 1215; mp 214 °C. CHNS Anal. Calcd for $C_{11}H_{15}N_3O_4$ as C, 52.17%; H, 5.97%; N, 16.59%. Found: C, 52.00%; H, 5.99%; N, 16.61%.
Compound **13**: ^{1}H NMR [$CDCl_3$, 200 MHz]: δ 1.34, 1.52 (2s, 6H), 3.71 (dd, 1H, $J = 8.59$, 4.26 Hz), 4.00 (ddd, 1H, $J = 3.33$, 8.78, 11.51 Hz), 4.23 (dd, 1H, $J = 10.90$, 13.32 Hz), 4.54 (d, 1H, $J = 15.14$ Hz), 4.80 (t, 1H, $J = 4.24$ Hz), 5.14 (d, 1H, $J = 15.10$ Hz), 5.31 (dd, 1H, $J = 2.73$, 13.02 Hz), 5.82 (d, 1H, $J = 3.52$ Hz), 7.59 (s, 1H); ^{13}C NMR [$CDCl_3$, 75 MHz]: δ 26.0, 26.2, 51.6, 62.9, 72.1, 78.5, 87.7, 103.4, 114.0, 133.9, 135.48; IR (cm^{-1}): 1465, 1377; mp 186 °C. CHNS Anal. Calcd for $C_{11}H_{15}N_3O_4$ as C, 52.17%; H, 5.97%; N, 16.59%. Found: C, 52.44%; H, 5.90%; N, 16.34%.