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# A tandem Ferrier and Click reaction: a facile synthesis of triazolyl-2,3-dideoxypyranosides

J. S. Yadav *, B. V. Subba Reddy, D. Narasimha Chary, Ch. Suresh Reddy

*Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 007, India*

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**Abstract**

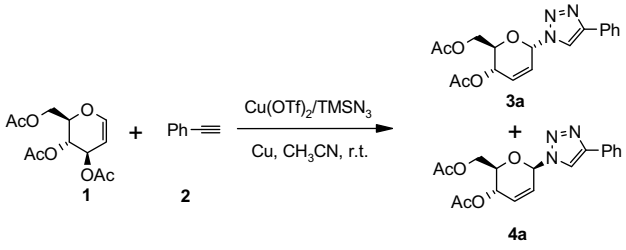
Glycosyl azides, prepared in situ from glucal and trimethylsilyl azide via Ferrier rearrangement, undergo smooth coupling with alkynes under neutral conditions by means of 'Click reactions' to furnish 1,2,3-triazole-linked glycoconjugates in high yields and with moderate stereoselectivity. The method provides a convenient route to prepare glycoconjugates from glucals, trimethylsilyl azide, and alkynes via a three component reaction.


*Keywords:* Glucal; Glycoconjugates; Alkynes; Click reaction; Triazoles

1,2,3-Triazoles are potential targets for drug discovery as they exhibit a broad spectrum of biological properties such as antiviral, antibacterial, antiepileptic, and antiallergic behavior.[1,2] They have also found applications as optical brighteners, light stabilizers, fluorescent whiteners, and corrosion-retarding agents.[3] The classical method for the preparation of 1,2,3-triazoles is the Huisgen reaction.[4] However, this uncatalyzed cycloaddition results in products with poor regioselectivity and low yields. The Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC),[5] one of the most reliable Click reactions,[6] has enabled the practical and efficient preparation of 1,4-disubstituted-1,2,3-triazoles, from a wide range of substrates with excellent selectivity, which cannot be attained with the traditional Huisgen uncatalyzed thermal approaches.[4] This powerful and reliable Cu-catalyzed 1,3-dipolar cycloaddition has found widespread applications in combinatorial chemistry for drug discovery,[7] material science,[8] and bioconjugation.[9,10] Since triazole-linked glycoconjugates have become increasingly useful and important in glycobiology, the development of a simple and efficient method for their synthesis in a single-step operation is desirable.

In this Letter, we report a direct one-pot method for the synthesis of triazole-linked glycoconjugates from readily available D-glucals, TMS azide, and alkynes involving a tandem Ferrier and Click reaction.[11] In a preliminary study, 3,4,6-tri-*O*-acetyl-D-glucal (**1**) was treated with trimethylsilyl azide and phenylacetylene (**2**) in the presence of 5 mol % of $Cu(OTf)_2$ and 10 mol % of metallic copper in acetonitrile (Scheme 1).

The reaction proceeded smoothly at room temperature and the product, 1,2,3-triazole-linked glycoside was obtained in 85% yield as a mixture of α-**3a** and β-**4a**




Scheme 1. Reaction of glucal, $TMSN_3$, and phenylacetylene.

* Corresponding author. Tel.: +91 40 27193535; fax: +91 40 27160512.
*E-mail addresses:* yadavpub@iict.res.in, yadav@iict.res.in (J. S. Yadav).

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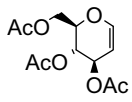
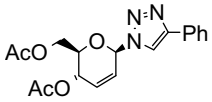
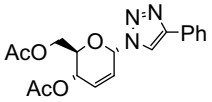
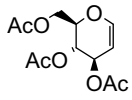
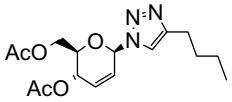
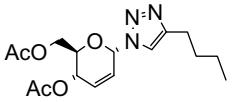
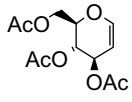
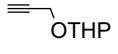
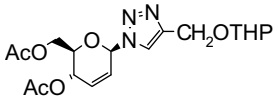
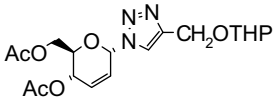
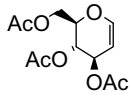
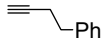
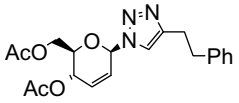
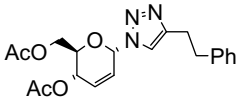
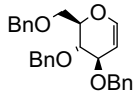
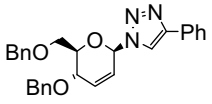
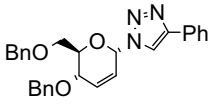
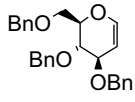
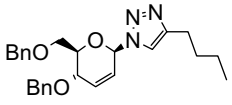
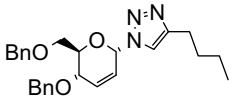
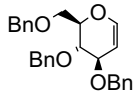
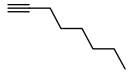
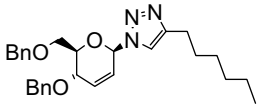
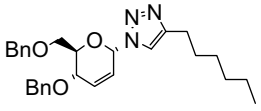
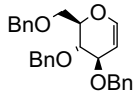
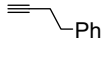
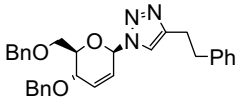
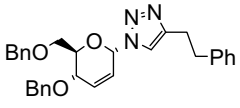
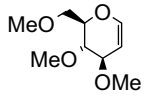
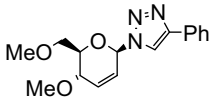
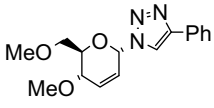
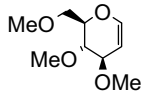
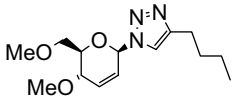
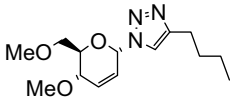
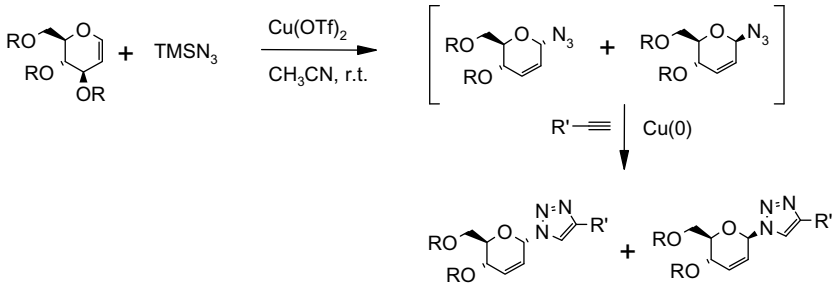
Table 1
Synthesis of triazole-linked glycosides via the Ferrier and Click reactions

| Entry | Glucal | Alkyne | Products[a] | | Time (h) | Yield[b] (%) | α:β |
|---|---|---|---|---|---|---|---|
| a |  |  |  |  | 4.5 | 85 | 3:2 |
| b |  |  |  |  | 5.0 | 80 | 4:1 |
| c |  |  |  |  | 5.0 | 70 | 7:3 |
| d |  |  |  |  | 4.5 | 75 | 7:3 |
| e |  |  |  |  | 4.5 | 85 | 3:2 |
| f |  |  |  |  | 5.5 | 80 | 9:1 |
| g |  |  |  |  | 6.0 | 80 | 4:1 |
| h |  |  |  |  | 5.5 | 70 | 3:2 |
| i |  |  |  |  | 4.5 | 80 | 3:2 |
| j |  |  |  |  | 5.0 | 75 | 4:1 |
| k |  |  |  |  | 6.0 | 70 | 7:3 |
| l |  |  |  |  | 6.5 | 65 | 4:1 |
| m |  |  |  |  | 6.5 | 65 | 7:3 |

[a] All the products were characterized by NMR, IR and mass spectrometry.
[b] Yield refers to pure products after chromatography.




Scheme 2. Formation of 1,2,3-triazole-linked 2,3-dideoxy-pyranoside.

Table 2
The effect of various solvents on the preparation of **3a/4a**[a]

| Entry | Solvent | Time (h) | Yield[b] (%) |
|---|---|---|---|
| 1 | $CH_3CN$ | 4.5 | 85 |
| 2 | $CH_2Cl_2$ | 5.0 | 80 |
| 3 | $CH_3NO_2$ | 6.0 | 72 |
| 4 | Toluene | 8.0 | 60 |
| 5 | THF | 6.0 | 65 |

[a] The ratio of **3a/4a** was 3:2.
[b] Isolated yield after chromatography.

isomers in a 3:2 ratio favoring the α-isomer **3a**. Stereoisomers **3a** and **4a** could be easily separated by column chromatography. This result provided the incentive for further study with various other alkynes such as 1-octyne, 1-hexyne, 4-phenyl-1-butyne, and a propargyl ether. These alkynes readily reacted with glycosyl azides under identical conditions to produce triazole-linked glycosides in high yields (Table 1, entries b–m).

Other glucal derivatives such as 3,4,6-tri-*O*-methyl, 3,4,6-tri-*O*-benzyl, 3,4,6-tri-*O*-TBS, and 3,4,6-tri-*O*-allyl-D-glucal also underwent smooth coupling with trimethylsilyl azide and alkynes to produce 1,2,3-triazole-linked 2,3-dideoxypyranosides in good yields. This method tolerates highly acid labile protecting groups such as THP and TBDMS ethers. However, in the absence of either copper triflate or copper(0), the reaction did not give the expected triazole even after long reaction times (8–12 h). Both copper triflate and copper metal are essential for the success of the reaction. As solvent, acetonitrile gives the best results. The scope and generality of this process is illustrated in Table 1.[12] The reaction may proceed via Ferrier rearrangement followed by [3+2] cycloaddition as depicted in Scheme 2.

The effects of various solvents were studied for the preparation of **3a** and **4a** and comparative results are presented in Table 2. No significant change in the ratio of products was observed in different solvents.

In conclusion, we have developed a direct one-pot glycosylation method for the synthesis of 1,2,3-triazole-linked glycoconjugates. By executing several reaction steps in a single step and purifying only at the final stage, this procedure avoids the isolation of the azide intermediate, which significantly reduces the reaction time and improves the overall yield. This method provides an easy access to a stable triazole linkage between carbohydrates and other functional groups and can be used as a new strategy for the bioconjugation of carbohydrates.

## Acknowledgment

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12. *Experimental procedure*: A mixture of glucal triacetate (0.5 mmol), $TMSN_3$ (0.6 mmol), and $Cu(OTf)_2$ (5 mol %) in acetonitrile (2 mL) was stirred at room temperature for 2 h. Then phenyl acetylene (0.55 mmol) and Cu powder (10 mol %) were added and the resulting mixture was stirred at room temperature for 2.5 h. After the completion of the reaction, as monitored by TLC, the product was extracted with ethyl acetate ($3 \times 10$ mL) and dried over anhydrous $Na_2SO_4$. Removal of the solvent in vacuo, followed by purification on silica gel using hexane–ethyl acetate (4:1) afforded the pure 1,2,3-triazole. *Spectral data for selected products*:

Compound **3a**: (2*R*,3*S*,6*S*)-2-[(acetyloxy)methyl]-6-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-3,6-dihydro-2*H*-3-pyranyl acetate: Solid; mp 104–106 °C, $[\alpha]_D^{27}$ 210 (*c* 0.7, chloroform); IR (KBr): $\nu_{max}$ 3452, 3136, 2925, 2854, 1745, 1652, 1458, 1370, 1227, 1076, 1048, 892, 768 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.76–7.90 (m, 3H), 7.19–7.51 (m, 3H), 6.80 (d, $J = 6.0$ Hz, 1H), 5.60 (t, $J = 5.2$ Hz, 1H), 5.23 (dd, $J = 5.2$, 6.5 Hz, 1H), 5.09 (t, $J = 5.2$ Hz, 1H), 4.09–4.35 (m, 3H), 2.05 (s, 3H), 2.04 (s, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 170.3, 169.6, 148.2, 128.8, 128.2, 125.6, 119.5, 95.2, 70.2, 66.5, 61.7, 52.1, 29.6, 20.5. LC–MS: *m*/*z*: 380 (M+Na). HRMS calcd for $C_{18}H_{19}N_3O_5Na$ ($M+Na^+$): 380.1222; found, 380.1215.

Compound **4a**: (2*R*,3*S*,6*R*)-2-[(acetyloxy)methyl]-6-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-3,6-dihydro-2*H*-3-pyranyl acetate: Solid; mp 112–114 °C. $[\alpha]_D^{20}$ −29.6 (*c* 0.8, chloroform). IR (KBr): $\nu_{max}$ 3465, 3136, 2927, 2855, 1743, 1655, 1455, 1371, 1234, 1097, 1037, 975, 764 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.93 (s, 1H), 7.78–7.87 (m, 2H), 7.22–7.47 (m, 3H), 6.20–6.38 (m, 3H), 5.38–5.46 (m, 1H), 3.89–4.28 (m, 3H), 2.12 (s, 3H), 2.06 (s, 3H).

Compound **3f**: (2*R*,5*S*,6*R*)-5-(benzyloxy)-6-[(benzyloxy)methyl]-5,6-dihydro-2*H*-2-pyranyl-4-butyl-1*H*-1,2,3-triazole: Liquid, $[\alpha]_D^{27}$ 169 (*c* 0.75, chloroform); IR (KBr): $\nu_{max}$ 3064, 3031, 2924, 2856, 1725, 1652, 1454, 1364, 1256, 1114, 1046, 744, 699 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 6.96–7.39 (m, 10H), 6.67 (d, $J = 6.0$ Hz, 1H), 5.47 (t, $J = 5.2$ Hz, 1H), 4.82–4.94 (m, 1H), 4.44–4.67 (m, 3H), 3.97–4.14 (m, 2H), 3.70 (d, $J = 3.0$ Hz, 2H), 2.71 (t, $J = 7.5$ Hz, 2H), 1.60–1.73 (m, 2H), 1.26–1.47 (m, 2H), 0.88–1.02 (m, 5H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 147.6, 146.4, 132.9, 128.4, 128.4, 127.9, 127.8, 127.7, 120.5, 119.9, 95.5, 73.6, 73.2, 72.1, 71.8, 68.4, 52.2, 31.4, 25.3, 22.3, 13.7. LC–MS: *m*/*z*: 456 (M+Na). HRMS calcd for $C_{26}H_{31}N_3O_3Na$ ($M+Na^+$): 456.2263; found, 456.2265.

Compound **3i**: 1-[(2*S*,5*S*,6*R*)-5-methoxy-6-(methoxymethyl)-5,6-dihydro-2*H*-2-pyranyl]-4-phenyl-1*H*-1,2,3-triazole: Solid; mp 102–104 °C. $[\alpha]_D^{27}$ 198 (*c* 0.5, chloroform); IR (KBr): $\nu_{max}$ 3421, 2923, 2853, 1726, 1652, 1460, 1215, 1091, 1043, 761 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.79–7.86 (m, 3H), 7.24–7.43 (m, 3H), 6.55–6.59 (m, 1H), 5.27–5.32 (m, 2H), 4.80–4.84 (m, 1H), 3.63–3.99 (m, 3H), 3.42 (s, 3H), 3.15 (s, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 148.0, 128.7, 127.9, 128.2, 125.8, 125.5, 119.4, 95.2, 74.1, 72.9, 70.6, 59.4, 57.9. LC–MS: *m*/*z*: 324 (M+Na). HRMS calcd for $C_{16}H_{19}N_3O_3Na$ ($M+Na^+$): 324.1324; found, 324.1327.

Compound **4i**: [(2*R*,5*S*,6*R*)-5-methoxy-6-(methoxymethyl)-5,6-dihydro-2*H*-2-pyranyl]-4-phenyl-1*H*-1,2,3-triazole: Solid; mp 108–110 °C. $[\alpha]_D^{20}$ −13.4 (*c* 0.5, chloroform); IR (KBr): $\nu_{max}$: 3447, 2923, 2852, 1650, 1460, 1243, 1112, 1046, 765 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.93 (s, 1H), 7.75–7.86 (m, 2H), 7.19–7.45 (m, 3H), 6.70 (dd, $J = 1.5$, 5.2 Hz, 1H), 5.51–5.57 (m, 2H), 4.93–4.98 (m, 1H), 3.81–4.05 (m, 3H), 3.52 (s, 3H), 3.41 (s, 3H).