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Multicomponent Cascade Transformation of D-Glucal to Furan-Appended Triazole Glycoconjugates

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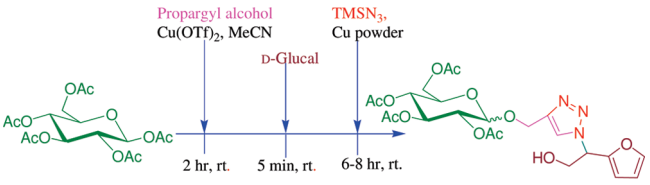
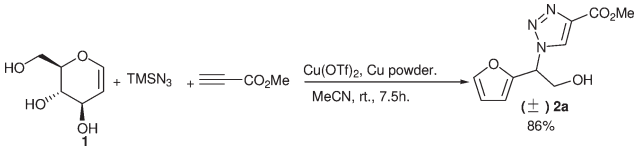


3a (86%) (dr 4:1)

Novel one-pot three- and four-component transformations of D-glucal to furan-based hydroxy triazole glycoconjugates have been achieved by sequential addition of reagents in the presence of $Cu(OTf)_2$−Cu powder as catalysts. In general the carbohydrate-derived products were formed with high diastereomeric purity.

At the interface between chemistry and biology, where so much new scientific insight, discovery, and development is being witnessed, the heterocyclic motifs dominate in more than 90% of the new drugs. The essential science upon which these advances are based is the synthesis of designed heterocyclic compounds which make it possible to probe sensitively the key events in biology in partnership with structural biology. The range of easily accessible and diversely functionalized heterocyclic building blocks is, however, surprisingly limited and there is still a need for novel and improved methodologies for constructing the molecular materials. Substituted furans represent a popular class of heterocycles with a number of pharmacological activities. Also these motifs exhibit their presence in innumerable natural and synthetic materials such as industrial intermediates, insecticides, flavors, and fragrances. In addition, they are widely used as precursors in synthetic chemistry.[1] Especially β-hydroxy α-furfuryl azide derivatives serve as important synthetic precursors in the preparation of numerous natural and synthetic compounds with significant biological activities.[2] In addition, these products can be converted to β-adrenergic receptor blocker analogues with furan-based hydroxy triazole moiety by employing click chemistry,[3] i.e., copper(I)-catalyzed azide−alkyne [3+2] cycloaddition.[4] Since hydroxytriazoles have become increasingly useful and important in drugs and pharmaceuticals,[5a,b] the development of improved methods for their synthesis with structural diversity is highly desirable. Although there are reports on the synthesis of hydroxy triazoles from epoxides[5a] via click reaction, the synthesis of furan-based hydroxy triazoles still remains a challenge.

SCHEME 1. One-Pot Synthesis of Furan-Based Hydroxy Triazole from D-Glucal



Multicomponent reactions[6] (MCRs), which combine two or more distinct reactions into a single transformation, present significant advantages over conventional linear step synthesis by reducing reaction time period and saving money, energy, and raw materials, thus resulting in both economical and environmental benefits. One-pot MC sequential synthetic methods, in which a number of synthetic steps involving two or more reactants are carried out in the same flask without the isolation of any intermediate, feature a high degree of reaction mass efficiency and are especially suitable in diversity oriented synthetic programs.

Traditionally, methods based on MC reactions have proved quite efficient for the construction of different arrays of heterocyclic compounds. One-pot MC reactions involving Knoevenagel condensation,[7a] Diels−Alder cycloaddition,[7b] Povarov reaction,[7c] Biginelli reaction,[7d] Passerini 3-component reaction,[7e] Ugi-4 condensation,[7f] Ritter−Prins reaction,[7g] and Cu(I)-catalyzed alkyne−azide[7h] coupling have been particularly explored. Despite these advances, there is a need to broaden the scope of carbohydrate-based one-pot MC reactions in combination with click chemistry. Since carbohydrates have secured their place in pharmaceutical chemistry,

(1) For importance and synthesis of substituted furans, see: Saquib,M.; Husain, I.; Kumar B.; Shaw, A, K. *Chem.—Eur. J.* **2009**, *15*, 6041 and refrences cited therein

(2) Mukherjee, D.; Yousuf, S. K.; Taneja, S. C. *Org. Lett.* **2008**, *10*, 4831 and refrences cited therein.

(3) (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004.

(4) Ankati, H.; Yang, Y.; Zhu, D.; Biehl, E. R.; Hua, L. *J. Org. Chem.* **2008**, *73*, 6433.

(5) (a) Yadav, J. S.; Reddy, B. V. S.; Reddy, G. M.; Chary, D. N. *Tetrahedron Lett.* **2007**, *48*, 8773. (b) Lee, T.; Cho, M.; Ko, S.-Y.; Youn, H.-J.; Baek, D. J.; Cho, W.-J.; Kang, C.-Y.; Kim, S. *J. Med. Chem.* **2007**, *50*, 585.

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(7) (a) Taha, N.; Sasson, Y.; Chidambaram, M. *Appl. Catal., A* **2008**, *350*, 217. (b) Powell, D. A.; Batey, R. A. *Tetrahedron Lett.* **2003**, *44*, 7569. (c) Kudale, A, A.; Kendall, J.; Miller, D. O.; Collins, J. L.; Bodwell, G. J. *J. Org. Chem.* **2008**, *73*, 8437. (d) Suzuki, I.; Iwata, Y.; Takeda, K. *Tetrahedron Lett.* **2008**, *49*, 238. (e) Fan, L.; Adams, A. M.; Ganem, B. *Tetrahedron Lett.* **2008**, *49*, 5983. (f) Thompson, M. J.; Chen, B. *Tetrahedron Lett.* **2008**, *49*, 5324. (g) Shao, L. X.; Qui, M.; Minshi, H. *Tetrahedron Lett.* **2008**, *49*, 165. (h) Jackson, D.; Megiatto, J.; Schuster, D. I. *J. Am. Chem. Soc.* **2008**, *130*, 8898.

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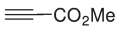
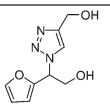
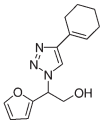
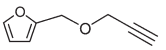
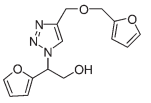
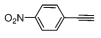
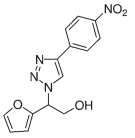
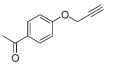
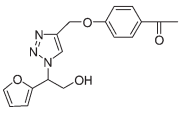
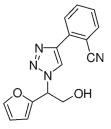
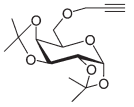
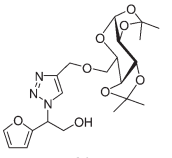
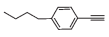
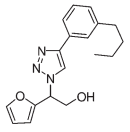
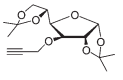
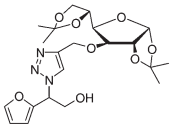
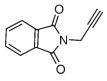
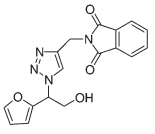
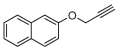
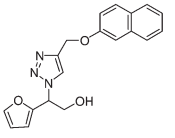
TABLE 1. Synthesis of α-Substituted Furan Derivatives from D-Glucal and Nucleophiles[c]

entry	alkyne	Product[a]	time (h)	Yield[b] (%)	entry	alkyne	Product[a]	time (h)	Yield[b] (%)
1		**2a**	7.5	86	7		 **2g**	7.5	80
2		 **2b**	8.2	84	8		 **2h**	7.5	80
3		 **2c**	8.0	83	9		 **2i**	7.5	82
4		 **2d**	7.8	80	10		 **2j**	7.5	85*
5		 **2e**	7.5	85	11		 **2k**	7.5	86**
6		 **2f**	8.0	84	12		 **2l**	7.5	85

[a]Characterized from ^{1}H and ^{13}C NMR. [b]Isolated yield. [c]In the last column (Yield): (*) dr = 90:10, (**) dr = 92:8 as determined from LCMS.

in biopharmaceuticals as well as in "small molecule" chemistry, they are more attractive substrates for the pressing demand in the present diversity oriented synthesis programs in combination with MC reactions. In carbohydrate chemistry Dondoni and co-workers have made significant contributions toward MCR.[8]

The screening process for new active principles critically depends on the availability of versatile compound libraries. MCRs are well suited to prepare libraries by variation of the individual components. Aiming at hydroxyl triazole compounds, we departed from activated carbohydrate components and explored new MCRs.

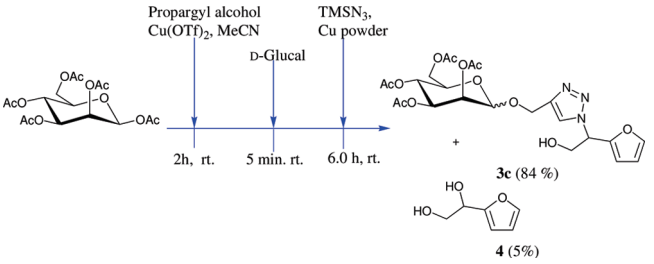
With our recent success in the development of one-pot tandem methodology in carbohydrate chemistry,[2,9] we envisioned that transformation of the easily available D-glucal (**1**) to racemic substituted furyl triazole derivatives can be completed in one pot without isolation of any intermediate. Further, by careful choice of the Lewis acid, an efficient cascade of several reactions can be performed in one pot, providing a high degree of atom-economy and complexity.

Earlier we have achieved direct conversion of D-glucal into α-azido furfuryl alcohol catalyzed by $In(OTf)_3$.[2] Gratifyingly, we observed that $Cu(OTf)_2$ can catalyze the same reaction as $In(OTf)_3$, which prompted us to design a one-pot synthetic strategy. To obtain evidence in favor of our hypothesis, a solution of D-glucal and $TMSN_3$ in acetonitrile was treated in a preliminary study with catalytic $Cu(OTf)_2$ and allowed to stir for 20 min. Then methyl propiolate and Cu powder were added successively to the same reaction mixture, which was stirred for 7.5 h (Scheme 1). The completion of the reaction was indicated by complete consumption of D-glucal. The presence of peaks at δ 8.14 (triazole), 7.4, 6.52, 6.4 (furan), and 3.8 (−OMe) in ^{1}H NMR, and 161.0, 147.6, 143.5, and 127.7 in ^{13}C NMR confirmed the formation of α-1,2,3-triazole-substituted furan moiety.

Gratifyingly, the degree of conversion was found to be the same when compared to the traditional sequential methodology. After getting positive results from the one-pot multicomponent transformation, the scope and generality of the reaction was expanded by varying the alkyne partner. Thus different sets of aromatic (electron rich as well as electron deficient), alicyclic, aliphatic O-/C-/N-substituted alkynes including sugar-derived ones (Table 1) were allowed to react with D-glucal and $TMSN_3$ under optimized conditions. In

(8) Dondoni, A.; Massi, A. *Acc. Chem. Res.* **2006**, *39*, 451.
(9) (a) Mukherjee, D.; Shah, B. A.; Gupta, P.; Taneja, S. C. *J. Org. Chem.* **2007**, *72*, 8965. (b) Thota, N.; Mukherjee, D.; Reddy, M. V.; Yousuf, S. K.; Koul, S.; Taneja, S. C. *Org. Biomol. Chem.* **2009**, *7*, 1280.

SCHEME 2. Reaction of D-Mannose, Propargyl Alcohol, D-Glucal, and $TMSN_3$



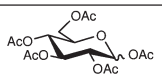
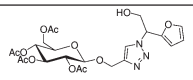
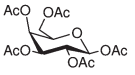
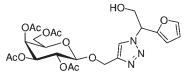
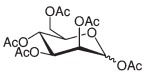
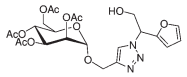
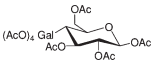
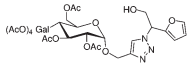
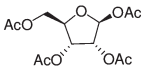
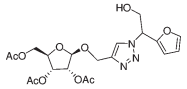
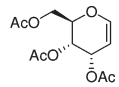
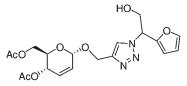
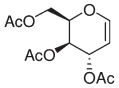
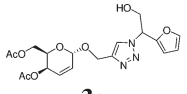
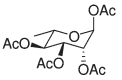
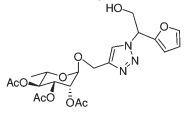
general the reaction rate of aromatic C-alkynes is comparable to that of their aliphatic counterparts (Table1, entries 1 and 2 vs entries 3, 4, and 5). In all the reactions including N- (entry 6, Table1) and O-derived alkynes, the yields were very good (>80%); the electronic nature of the alkyne had negligible effect on the rate as well as the regioselectivity of the reaction.

Triazole-*O*-glycosides have long been used as fluorescence[10] probes and anticancer agents.[11] However, synthesis of this class of glycoconjugates involves Lewis acid-catalyzed glycosylation of glycosyl donors to obtain α/β-anomeric mixtures, which are further subjected to copper-mediated azide alkyne cycloaddition to generate glycoconjugate libraries. With the modified 3-component one-pot procedure in hand, we then explored the possibility of extending the "tandem" process further by sequential addition of reagents that could become active under $Cu(OTf)_2$ catalysis to generate biologically important furan-appended triazole glycoconjugates. We envisioned that by fine-tuning the reaction conditions, both sugar−alkyne and azide partners can be generated in situ, which thereafter may undergo Huisgen's cycloaddition[4] under the same Lewis acidic condition to make it practically a four-component reaction. To obtain practical evidence in favor of our notion, a solution of pentaacetylated D-mannose and propargyl alcohol in acetonitrile was subjected to *O*-glycosylation under $Cu(OTf)_2$ activation, followed by sequential addition of D-glucal, $TMSN_3$, and finally copper powder to afford the triazole **3c** (Scheme 2) as the major product in good yield (84%) along with furan diol (**4**) as the side product (5%).

Other glycosyl donors also reacted in the similar fashion to yield structurally diverse glycocongugates in moderate yield (Table 2, entries 2, 3, 4, and 5). Further, taking advantage of $Cu(OTf)_2$-mediated Ferrier transformation,[12] rapid one-pot synthesis of triazole-linked glycocongugates has also been accomplished from readily available glycal derivatives (Table 2, entries 6 and 7). The structure of newly formed furan-based hydroxy triazolyl glycoconjugate was determined from $^1H-^1H$ COSY, HMBC, and HSQC experiments. The observed HMBC correlations H1/C1′, H1′/C3′, H6″/C2″, H1″/C3′, and H1″/C3″ are in complete accord with the proposed structure (Figure 1).

To our surprise we obtained the products with high distereoselective control, though there is a possibility of formation of four diastereomers. Simple silica gel column chromatographic purification failed to separate the diastereomers. However, after several attempts we could separate the diastereomers using LCMS-reverse phase chromatography. With anomeric selectivity of all the derivatives almost ~100% (as observed from ^1H NMR given in Supporting Information), it was apparent that the formation of the new stereogenic center at the α-position of the furan ring led to the formation of two diastereomers with one in preponderance. Similar results were obtained in 3-component reactions where sugar templates have been used as alkyne partners (Table 1 entries 10 and 11) The high diastereoselectivity of

TABLE 2. Copper-Mediated Synthesis of Furan-Based Glycocongugates

entry	glycosyl donor	product[a]	t (h)	Yield[b] (dr)[c]
1		 **3a**	7.5	86(4:1)
2		 **3b**	8.2	84(6:1)
3		 **3c**	8.5	84(7:1)
4.		 **3d**	8.5	74(4:1)
5.		 3e	7.5	79(6:1)
6		 **3f**	7.8	80 (4:1)
7.		 **3g**	7.5	82 (4:1)
8.		 **3h**	7.0	85 (8:1)

[a]Products obtained with use of glycosyl donor (1 equiv), propargyl alcohol (1.2 equiv), D-glucal (1 equiv), and $TMSN_3$ (1.5 equiv). [b]Isolated yield after column chromatography. [c]dr values have been determined from LCMS.

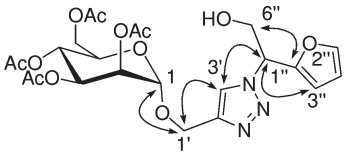
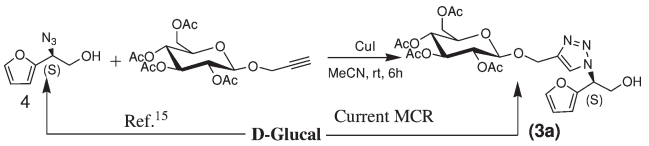


FIGURE 1. Determination of furan-based hydroxy triazolyl glycoconjugate structure by 2D NMR.

(10) Sawa, M.; Hsu, T.-L.; Itoh, T.; Sugiyama, M.; Hanson, S. R.; Vogt, P. K.; Wong, C.-H. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 12371.
(11) Wilkinson, B. L.; Bornaghi, L. F.; Houston, T. A.; Innocenti, A.; Vullo, D.; Supuran, C. T.; Poulsen, S. A. *J. Med. Chem.* **2007**, *50*, 1651.
(12) Mukherjee, D.; Yousuf, S. K.; Taneja, S. C. *Tetrahedron Lett.* **2008**, *49*, 4944.

SCHEME 3. Determination of Absolute Configuration at the α-Position of the Furan Ring



In the present multicomponent reaction, it needs to be

the products may be attributed to the presence of the sugar template, which may direct the formation of a particular diastereomer predominantly. Though sugar residue is far away from the chiral center, there is ample evidence that the sugar residue is involved in a high level of remote asymmetric inductions.[13]

To assign[14] the stereochemistry at the newly derived furan-substituted stereogenic center of the major diastereomer, enantiomerically pure (*S*)-2-(*tert*-butyldiphenylsilyloxy)-1-(2-furyl)ethyl azide has been synthesized following the literature procedure.[15] Deprotection of the TBDPS group resulted in enantiomerically pure **4** having *S*-configuration (ee, 98%), which was further reacted with anomerically pure sugar alkynes to obtain diastereomerically pure furan-appended triazole glycoconjugates (**3a**−**h**). The specific rotation values as well as LCMS profiles of resulting products were compared with those of the compounds synthesized by using the current MCR methodology (see the Supporting Information) and accordingly the newly developed stereogenic center in all the compounds was assigned the *S*-configuration (Scheme 3).

In the present multicomponent reaction, it needs to be emphasized that use of both $Cu(OTf)_2$ and Cu powder is necessary as we failed to obtain the desired products in the absence of either of the two.

On the basis of our earlier experimental studies,[2] the one-pot formation of hydroxy triazole can be explained by the $Cu(OTf)_2$-mediated in situ generation of racemic furfuryl azide from D-glucal followed by the Cu(I) (generated in situ by the redox reaction $Cu^{2+} + Cu^0 \rightarrow Cu^{1+}$) catalyzed 1,3 dipolar alkyne−azide cycloaddition. In the case of four-component reactions, $Cu(OTf)_2$ is also catalyzing glycosylation, besides azide formation, thus making this cascade reaction atom economic.

In summary, we have developed a novel $Cu(OTf)_2$/Cu powder-mediated one-pot reaction for synthesizing highly substituted hydroxy triazoles from the easily available D-glucal. To the best of our knowledge this is the first report of synthesizing furan-based hydroxy triazoles. The study has led to the development of a Lewis acid-catalyzed multicomponent reaction culminating in one-pot construction of highly functionalized motifs from carbohydrate precursors as represented in diversity oriented synthesis. Future work will address the exploration of this principle in the construction of other highly substituted heterocyclic natural product skeletons.

Experimental Section

A typical procedure for four component reactions follows: Propargyl alcohol (0.307 mmol, 17 mg) and $Cu(OTf)_2$ (10 mol %) were added to a stirred solution of α-D-mannose pentaacetate (100 mg, 0.256 mmol) in acetonitrile (5 mL). The reaction mixture was allowed to stir for 2.5 h. D-Glucal (37 mg, 0.256 mmol) and $TMSN_3$ (0.384 mmol) were added successively followed by the addition of 10 mol % of Cu powder. The reaction mixture was stirred for the specified time (Table 2) at room temperature. The completion of reaction was confirmed through TLC (complete consumption of D-mannose pentaacetate). The reaction mixture was passed through Celite, concentrated, and subjected to column chromatography (hexane:ethyl acetate, 20:80) over silica gel (60−120 mesh size) to afford the product **3c** (84%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.7 (s, 1H, H-3′), 7.4 (s, 1H, H-6′), 6.39 (dd, J = 3.2, 2.0 Hz, 1H, H-4″), 6.51−6.49 (m, 1H, H-5″), 5.87 (dd, J = 7.0, 4.7 Hz, 1H, H-1″), 5.29 (d, J = 1.33 Hz, H-2), 5.28 (d, J = 2.2 Hz, 1H, H-4), 5.20 (m, 1H, H-3), 4.94 (dd, J = 1.36, 4.21 Hz, 1H, H-1), 4.78 (dd, J = 4.5, 12.4 Hz, 1H, H-2a), 4.65 (m, 1H, H-2a″), 4.45−4.39 (m, 1H, H-6b), 4.28−4.24 (m, 2H, H-6a, H-1a′), 4.08−4.05 (m, 2H, H-5, H-1b′), 2.13 (s, 3H, COCH3), 2.08 (s, 3H, $COCH_3$), 2.04 (s, 3H, $COCH_3$), 1.97 (s, 3H, $COCH_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.8, 170.7, 170.1, 169.5 (4 × −CO), 148.5 (C-3″), 143.8 (C-2′), 143.2 (C-6″), 123.1 (C-3′), 110.6 (C-5″), 109.6 (C-4″), 96.9 (C-1), 69.4 (C-3), 68.9 (C-2), 68.0 (C-5), 65.9 (C-4), 62.9 (C-6), 62.1 (C-1′), 60.9 (C-2″), 60.2 (C-1″), 20.6, 20.5, 20.4, 20.3 (4 × $COCH_3$); ESI MS (m/z) 562 $[M + Na]^+$. Anal. Calcd for $C_{23}H_{29}N_3O_{12}$: C, 51.21; H, 5.42; N, 7.79. Found C, 51.06; H, 5.23; N, 7.56.

Acknowledgment. This work is supported by CSIR, India.

Supporting Information Available: Compound characterization data, including copies of ^{1}H and ^{13}C 2D NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

(13) (a) Dondoni, A.; Massi, A.; Sabbatini, S. *Tetrahedron Lett.* **2002**, *43*, 5913. (b) Togo, H.; Ishigami, S.; Fujii, M.; Ikuma, T.; Yokoyama, M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1931. (c) Huber, R.; Vasella, A. *Tetrahedron* **1990**, *46*, 33. (d) Kishida, M.; Eguchi, T.; Kakinuma, K. *Tetrahedron Lett.* **1996**, *37*, 2061. (e) Ewing, D. F.; Len, C.; Mackenzie, G.; Ronco, G.; Villa, P. *Tetrahedron: Asymmetry* **2000**, *11*, 4995.

(14) Assignment of the stereochemistry has been carried out as suggested by one of the reviewers.

(15) Koulocheri, S. D.; Haroutounian, S. A. *Synthesis* **1999**, *11*, 1889.