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Domino Transformation of D-Glucal to Racemic α-Substituted α-Hydroxymethyl Furfuryl Derivatives

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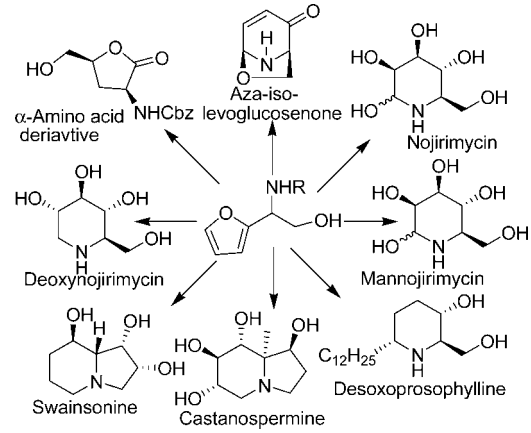
ABSTRACT

Lewis acid mediated one-pot transformation of D-glucal in the presence of nucleophiles leads to the formation of racemic α-substituted α-hydroxymethyl furfuryl derivatives, versatile synthons for biologically active molecules. Transformations using O-, S-, C-, and N-nucleophiles could be achieved readily under mild and scalable conditions. Indium triflate proved to be the catalyst of choice in terms of conversion and regioselectivity.

α-Substituted α-hydroxymethyl furfuryl derivatives[1] are valuable synthons for the preparation of numerous natural and synthetic bioactive molecules related to anti-HIV, anti-cancer, anti-arthritic, anti-inflammatory, anti-diabetic, and glucosidase inhibitory activities. Especially, α-furfuryl amine derivatives[2] are very useful building blocks for the synthesis of a large number of nitrogen-containing natural products (Scheme 1).

In recent years, furan chemistry has been enriched by the development of newer synthetic approaches that are more versatile and practicable.[3] A large number of methods are available in the literature for the synthesis of α-substituted α-hydroxymethyl furfuryl derivatives, based either on carbohydrate[1c,4c] or more preferably noncarbohydrate precursors,[4] such as functionalized furans (Scheme 2).

Scheme 1. Examples of Biologically Important Molecules Generated from α-Furfuryl Amine Derivative[2]



Most of these synthetic transformations require multiple reaction steps and therefore lack wide applicability. Notably,

(1) (a) Ostrowski, J.; Altenbach, H.-J.; Wischnat, R.; Brauer, D. J. *Eur. J. Org. Chem.* **2003**, 1104–1110. (b) Koulocheri, S. D.; Magiatis, P.; Haroutounian, S. A. *J. Org. Chem.* **2001**, *66*, 7915–7918, and references therein. (c) Saeed, M.; Ilg, T.; Schick, M.; Abbas, M.; Voelter, W. *Tetrahedron Lett.* **2001**, *42*, 7401–7403.

(2) (a) Liao, L.-X.; Wang, Z.-M.; Zhang, H.-X.; Zhou, W. S. *Tetrahedron: Asymmetry* **1999**, *10*, 3649–3657. (b) Altenbach, H.-J.; Wischnat, R. *Tetrahedron Lett.* **1995**, *36*, 4983–4984. For a review on the preparation of asymmetric α-furfurylamines and their synthetic applications, see: (c) Zhou, W.-S.; Lu, Z.-H.; Xu, Y.-M.; Liao, L.-X.; Wang, Z. M. *Tetrahedron Lett.* **1999**, *55*, 11959–11983. (d) Xu, Y.-M.; Zhou, W.-S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 741–751.

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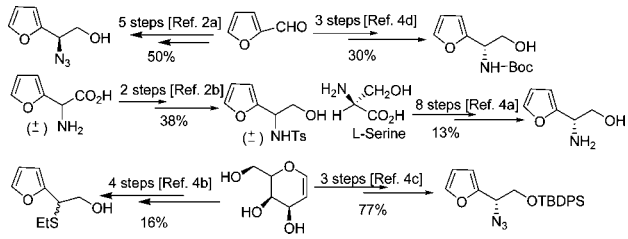
Scheme 2. Syntheses of α-Substituted β-Hydroxyfurfuryl Derivatives in the Literature

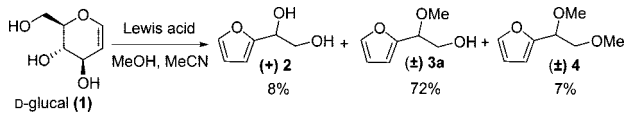


earlier attempts at Lewis acid catalyzed α-substitution of furfuryl derivatives by direct nucleophilic attack was not successful due to the degradation of the acid-sensitive furfuryl residue.[5] The development of a more flexible and direct approach for the construction of a furfuryl scaffold is therefore highly desirable. Our group, which has been involved in synthesizing orthogonally protected building blocks from carbohydrate precursors,[6] now reports the development of a short and rapid one-pot domino chemoselective synthesis of racemic furfuryl derivatives from D-glucal.

Acid-catalyzed transformation of D-glucal to optically active furan diol[7] is a well-studied reaction. Nucleophilic attack of water on D-glucal was proposed to be the possible mechanism.[7c] Under similar conditions, L-rhamnal gave a complex mixture of optically inactive furan tetramers.[7e] On the other hand, a protected glycal undergoes Ferrier rearrangement[8] and a partially protected glycal follows an addition pathway when reacted with nucleophiles in presence of Lewis acid.[9] However, the behavior of nucleophiles toward unprotected glucal has not been studied in details. The only report available to date describes prolonged treatment of D-glucal with methanolic HCl, which resulted in the formation of a racemic furan derivative, i.e., 2-hydroxymethyl-5-methoxy furan in poor yield.[7h]

We, therefore, envisaged that a nucleophile other than water may deliver a different type of product with an unprotected glucal. Accordingly, glucal was stirred in acetonitrile using methanol as a nucleophile under standard Lewis acid conditions at ambient temperature. Surprisingly, no methyl glycoside formation was observed. Instead, a mixture comprising two racemic compounds and a minor optically active furan diol **2** was obtained (Scheme 3). The

Scheme 3. Unexpected Reaction of D-Glucal with Methanol



major product was identified as a racemic α-furfuryl derivative **3a** from the ^{1}H NMR spectrum.

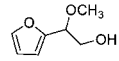
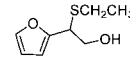
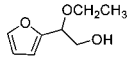
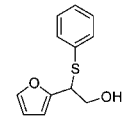
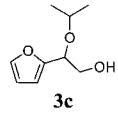
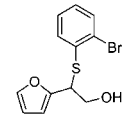
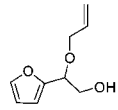
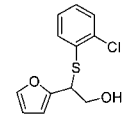
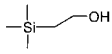
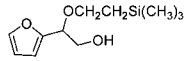
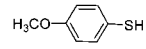
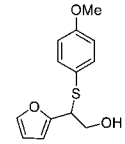
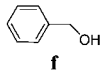
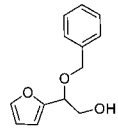
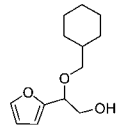
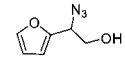
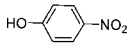
Synthetic transformations from chiral pool precursors such as carbohydrates generally lead to the formation of optically active products. However, it was surprising for us to obtain racemic products under the present reaction conditions. Though exceptional, it was yet considered advantageous, as both the enantiomers can be obtained through kinetic resolution using the literature procedures.[10] Especially, concomitant nucleophilic substitution at the α-position is the most significant outcome of the present domino reaction. Besides, the racemic α-substituted furan moiety can be directly utilized in the preparation of antibiotics such as (±)-1-deoxygulonojirimycin[1a] and (±)-mannojirimycin.[2b]

For optimization, catalytic efficacies of various Lewis acids were screened for the desired conversions (see Supporting Information, Table 1). It was observed that $In(OTf)_3$ in acetonitrile (1 mol %) was superior to other catalysts with regard to yield, reaction time, and minimal side product formation (**2**, **4**). High regioselectivity was observed in polar aprotic solvents, and acetonitrile was found to be the best (see Table 2 in Supporting Information). Substituting methanol with an aprotic nucleophile such as $TMSN_3$ yielded (±)-2-hydroxy-1-(2-furyl)ethyl azide (**3o**), an important intermediate for many azasugar antibiotics,[2d] as the major product (80%) (Table 1 entry **15**). It may be noted that Vincent et al. failed to obtain such a product while working with α-furyl benzyl alcohol and $TMSN_3$.[5] The nucleophilic substitution reaction with $TMSN_3$ can also be carried out smoothly in water with longer reaction time. Besides, the reaction could also be catalyzed by montmorillonite KSF or H_2SO_4 on silica at an elevated temperature (80 °C) to yield **3o**, though in poor yield. Likewise, D-galactal also readily reacted with this reagent system, forming **3o** in 72% yield in 1 h.

After establishing the reaction protocol, we further explored the scope and the generality of the method using various O, S, or N nucleophiles (see Supporting Information, Figure 1) for the preparation of a small library of furfuryl analogues **3a**−**o**. The free amine, however, failed to react at all (entry 14). As expected, the thiols reacted faster than the alcohols and all the reactions were completed within 20 min, requiring less than 1 mol % of the catalyst. The electronic nature of the nucleophiles seems to have a modest influence on the rate of the reaction (Table 1, entries 10−13). It was also observed that the use of alcohols larger than methanol generally led to an increase in the formation of α-substituted products (Table 1, entries 2−7). Significantly, with

(3) Brown, R. C. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 850–852.
(4) (a) Xin, C.; Ke-Gang, L.; Qing-Jiang, L.; Zhu-jun, Y. *Tetrahedron Lett.* **2005**, *46*, 8567–8571, and references therein. (b) Porzelle, A.; Gardon, V. A.; Williams, C. M. *Synlett* **2007**, 1619–1621. (c) Koulocheri, S. D.; Haroutounian, S. A. *Synthesis* **1999**, 1889–1892. (d) Yang, J. W.; Chandler, C.; Stadler, M.; Kampen, D.; List, B. *Nature* **2008**, *452*, 453–455. (e) Liao, L.-X.; Wang, Z.-M.; Zhang, H.-X.; Zhou, W. S. *Tetrahedron: Asymmetry* **1999**, *10*, 3649–3657. (f) Alcaide, B.; Biurrum, C.; Plumet, J. *Tetrahedron* **1992**, *48*, 9719–9724.
(5) Tarrasson, V.; Marque, S.; Georgy, M.; Campagne, J.-M.; Prim, D. *Adv. Synth. Catal.* **2006**, *348*, 2063–2067.
(6) Mukherjee, D.; Shah, B. A.; Gupta, P.; Taneja, S. C. *J. Org. Chem.* **2007**, *72*, 8965–8968.

Table 1. Synthesis of α-Substituted Furan Derivatives from D-Glucal and Nucleophiles

entry	NuH[a]	product[b]	time [h]	yield[c][%]	entry	NuH[a]	product[b]	time [h]	yield[c][%]
1	MeOH **a**	 **3a**	3	76	9	EtSH **i**	 **3i**	0.3	79
2	EtOH **b**	 **3b**	3.5	79	10	PhSH **j**	 **3j**	0.2	85
3	Me_2CHOH **c**	 **3c**	2.5	78	11	 **k**	 **3k**	0.2	83
4	 **d**	 **3d**	2.7	80	12	 **l**	 **3l**	0.2	80
5	 **e**	 **3e**	3.5	75	13	 **m**	 **3m**	0.2	85
6	 **f**	 **3f**	3	78	14	Me_2NH **n**	-	6	0
7	 **g**	 **3g**	3	76	15	$TMSN_3$ **o**	 **3o**	0.2	80
8	 **h**	-	6	0	16	EtMgBr **p**	-	6	0

[a] 1 mol % $In(OTf)_3$ and 1.5 equiv of NuH used. [b] Characterized from ^1H and ^{13}C NMR. [c] Isolated yield.

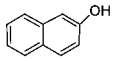
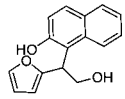
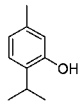
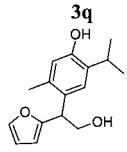
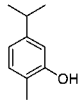
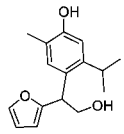
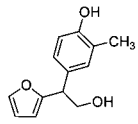
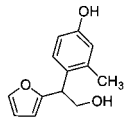
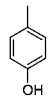
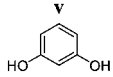
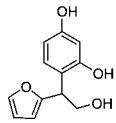
β-naphthol as a nucleophile, the formation of a C−C bond at the α-position was observed with 80% yield. The C−C bond formation was confirmed by ^1H and ^{13}C NMR data of the corresponding diacetate (see Table 2, entry 1 and Supporting Information for spectral data).

Encouraged by the results obtained from β-naphthol, we also explored the use of various substituted phenolic compounds as a source of carbon nucleophiles. Thus *o*-, *m*-, *p*-cresol, resorcinol, and naturally occurring phenols such as thymol and carvacrol were reacted with D-glucal under optimized reaction conditions. In all these reactions (Table 2, entries 1−7), a facile furano substitution occurred *para* to the hydroxy group (except with *p*-cresol, which failed to react and β-naphthol, which gave an *o*-substituted product) as established from NMR. For example, the presence of signals at δ 7.00 (br s), 6.95 (dd, J = 8.1, 1.8 Hz), and 6.69 (d, J = 8.1 Hz) in the ^1H NMR of **3t** implied the formation of a C−C bond *para* to the OH in *o*-cresol (Table 2, entry 4). As anticipated, a stronger activating phenolic group directed the formation of the C−C product. On a larger scale (20 mmol of the substrate), the reaction proceeded in a similar manner even with a lower catalyst loading (0.5 mol %), thus making the process amenable to easy scale up.

On the basis of our experiments and the earlier proposed mechanism, [7c] the formation of a racemic product in the domino reaction may be explained in the following way.

The racemization probably occurs after the formation of furan derivative. The Lewis acid may induce the elimination of the substituent from the α -position (possibly with the participation of furan oxygen, Scheme 4) to form a carbonium ion, which after nucleophilic attack

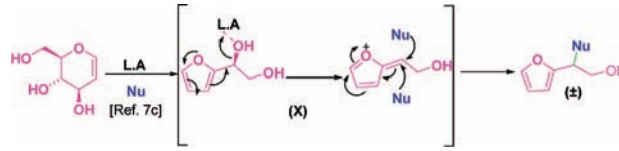
Table 2. Synthesis of α-Substituted Furan Derivatives from D-Glucal and Phenolic Nucleophiles

entry	nucleophile[a]	product[b]	time [h]	yield[c][%]
1	 **q**	 **3q**	6	80
2	 **r**	 **3r**	3	83
3	 **s**	 **3s**	2.5	79
4	 **t**	 **3t**	3.5	82
5	 **u**	 **3u**	3	78
6	 **v**	-	6	0
7	 **w**	 **3w**	3.5	81

[a] 1 mol % $In(OTf)_3$ and 1.5 equiv nucleophile used. [b] Characterized from ^1H and ^{13}C NMR. [c] Isolated yield.

leads to the generation of a racemic product. Indeed, in a control experiment, the reaction of the optically active

Scheme 4. Plausible Mechanism of Lewis Acid Mediated Formation of Substituted Furan from D-Glucal



furan diol led to the formation of the expected recemized nucleophilic substitution product.

In summary, we have developed a novel one-pot domino method for the rapid transformation of D-glucal to racemic α-substituted α-hydroxymethyl furfuryl derivatives in the presence of a catalytic amount of indium triflate under facile and mild reaction conditions. The possible range of down stream products derived from nucleophile-substituted furfuryl derivatives is enormous.

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Supporting Information Available: Experimental procedure and NMR spectra.This material is available free of charge via the Internet at http://pubs.acs.org.

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