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Tetrahedron Letters 47 (2006) 2021–2023
Tetrahedron Letters

Stereoselective synthesis of α-glucosides from 3-*O*-propargyl protected glucal exploiting the alkynophilicity of $AuCl_3$

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Received 23 November 2005; revised 20 December 2005; accepted 12 January 2006
Available online 3 February 2006

Abstract—The stereoselective synthesis of 2,3-unsaturated α-D-glucosides by the S_N2' addition of diverse aglycones onto 4,6-di-*O*-benzyl-3-*O*-propargyl glucal was achieved using a catalytic quantity of $AuCl_3$. The Au catalyzed reaction was explored using various aliphatic, aromatic, alicyclic and monosaccharide aglycones. The current protocol tolerates diverse functional groups and is highly stereoselective, fast, catalytic and mild.

Glycals are excellent templates for initiating diversity oriented synthesis[1] to achieve stereochemically pure compound libraries possessing unique structural architecture and complexity.[2] One type of important chiral intermediate that can be obtained from glycals is 2,3-unsaturated glycosides. Various natural products,[3] glycopeptides,[4] natural product-like compounds,[2b] modified carbohydrate derivatives,[5] nucleosides and oligosaccharides[6] were synthesized involving 2,3-unsaturated glycosides as key intermediates. The 2,3-olefinic group in the pyran rings can be diversified by a number of complexity generating reactions such as asymmetric dihydroxylation, amino hydroxylation, hydrogenation and epoxidation in order to achieve structural diversity.[7] 2,3-Unsaturated glycosides are routinely synthesized via S_N2' addition of alcohols onto per-*O*-acetylated glycal in the presence of a Lewis acid, a process known as the Ferrier reaction.[8]

In our programme[2b,8c,9] directed towards the development of diversity oriented synthesis of oxygen-rich chemical scaffolds, we considered performing alkoxycyclization[10] on 3-*O*-propargyl bearing glucal **1** by chemoselective activation of the terminal alkyne exploiting the alkynophilicity of Au to afford scaffold **2** (Fig. 1).[11] We disclose in this letter our observations which demonstrated that a Ferrier-like reaction takes place even with a propargyl group in the C-3 position of the glucal.

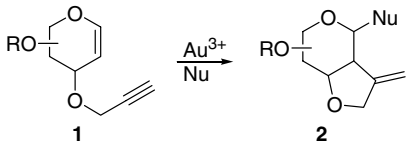

Figure 1. Au-mediated alkoxycyclization.

To begin our investigation, the easily accessible glucal **3** was converted to 4,6-di-*O*-benzyl glucal **4**[12] which was then transformed to the corresponding 3-*O*-propargyl derivative **5** using NaH/propargyl bromide/*n*-Bu_4NI in 90% yield (Scheme 1). Subsequently, an acetonitrile solution of **5** was treated with 3 mol % $AuCl_3$ in acetonitrile in the presence of methanol at 80 °C for 4 h.

Surprisingly, we found that the reaction did not result in the formation of any alkoxycyclized product but instead the S_N2' addition product **6a** in 38% yield with 50% recovery of the starting material **5**. In the ^1H NMR spectrum of the product of the Au-mediated reaction, resonances due to the olefin moiety were observed between δ 5.62 and 6.10 ppm and the methoxy group was identified at δ 3.44 ppm as a sharp singlet. Furthermore, the ^{13}C NMR spectrum showed that the olefinic carbons were at δ 126.5 and 130.8 ppm and the anomeric carbon was evident at δ 95.7 ppm. However, the DEPT NMR spectrum revealed that there was no methylene group in the olefinic region which confirmed that the resultant product was the 2,3-unsaturated methyl glucoside **6a**.[13,8c] Mechanistically, the alkynophilic Au^{3+} activated the triple bond to make the propargyl moiety a leaving

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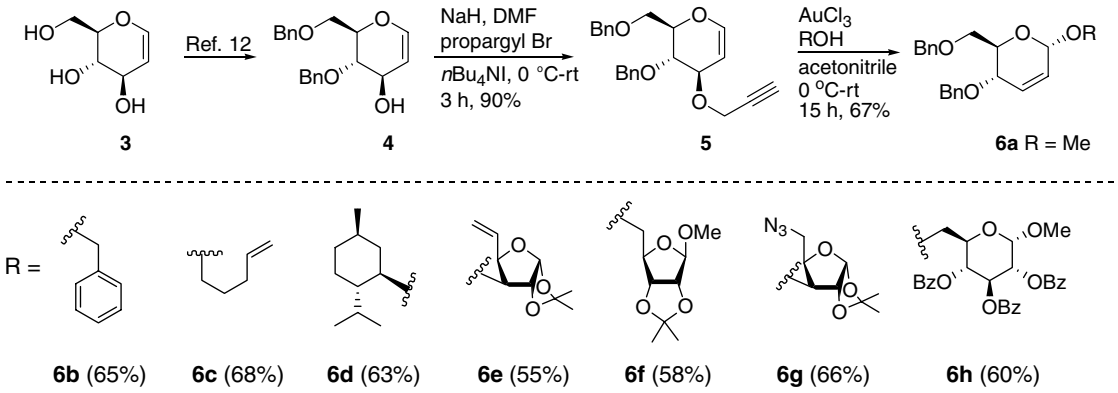
doi:10.1016/j.tetlet.2006.01.048



Scheme 1. Synthesis of a range of 2,3-unsaturated α-D-glucosides from 4,6-di-*O*-benzyl-3-*O*-propargyl glucal.

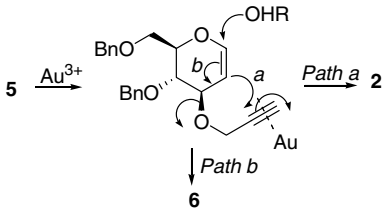


Figure 2. Mechanism.

group thereby leading to a Ferrier-like reaction (Fig. 2, path b) instead of trapping the Au–alkyne complex via an alkoxycyclization (Fig. 2, path a).

The overall yield of the reaction was enhanced to 67% when the reaction was carried out at 0 °C–rt for 15 h with 5 mol % of $AuCl_3$ under an argon atmosphere.[14] Having identified that propargyl ethers can act as a leaving group in the Au catalyzed S_N2' reaction, we performed parallel syntheses of 2,3-unsaturated α-glucosides using a diverse range of aglycones. Thus compound **5** was treated with various aglycones to afford aromatic **6b**, aliphatic **6c**, alicyclic **6d** and monosaccharidic (**6e**–**h**) 2,3-unsaturated α-glucosides in good yields (Scheme 1).[13,14] It should be noted that the current methodology tolerates various functional groups such as olefin (**6c**,**e**), isopropylidene (**6e**–**g**), azide **6g** and esters **6h**.

In summary, we have identified for the first time that the alkynophilicity of Au(III) promotes a Ferrier-like reaction when 3-*O*-propargyl bearing glucal was treated with $AuCl_3$ in the presence of aglycones. The utility of the methodology was established using a diverse range of aglycones and the synthesis of more compounds exploiting pentenyl glucoside **6c** for our diversity oriented synthesis programme is currently underway. It is pertinent to mention that the $AuCl_3$ mediated reaction is stereoselective, moisture tolerant and catalytic.

Acknowledgements

S.H. thanks the DST, New Delhi (SR/S1/OC-06/2004), for financial support. S.H. is grateful for the encouragement of Dr. K. N. Ganesh. S.K. acknowledges a fellowship from CSIR-New Delhi.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.01.048.

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13. All products gave satisfactory ^{1}H, ^{13}C, DEPT NMR (see supporting information) and CHNS analysis.
14. General experimental procedure: To a solution of compound **5** (1 mmol) in anhydrous acetonitrile (5 mL) was added aglycone (2 mmol) and $AuCl_3$ (5 mol % in acetonitrile) at 0 °C and the resulting mixture stirred at rt for 15 h. The reaction mixture was concentrated in vacuo, the crude residue was redissolved in ethyl acetate and washed with water. The organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and the resulting residue was purified by silica gel column chromatography using light petroleum (60–80 °C) and ethyl acetate to afford the 2,3-unsaturated α-glucosides in good yields.