JOC*Note*

Protic Acid ($HClO_4$ Supported on Silica Gel)-Mediated Synthesis of 2,3-Unsaturated-*O*-glucosides and a Chiral Furan Diol from 2,3-Glycals

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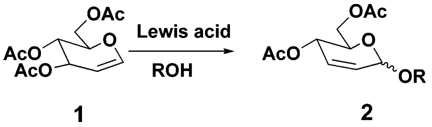
Abstract: Perchloric acid supported on silica gel acts as an excellent reagent system in converting glucals into 2,3-unsaturated-*O*-glucosides in good to excellent yields in short reaction time with good α selectivity. Primary, secondary, and allylic alcohols, phenols, and thiols react with 3,4,6-tri-*O*-acetyl glucal with equal ease. In addition to this, a chiral furan diol is obtained from unprotected D-glucal or D-galactal in good yields.

2,3-Unsaturated-*O*-glycosides are useful chiral intermediates[1] in the synthesis of biologically active compounds such as glycopeptide building blocks,[2] oligosaccharides,[3] and modified carbohydrates.[4] They have also been employed in the synthesis of some important antibiotics[5] and nucleosides.[6] 2,3-Unsaturated-*O*-glycosides **2** (Scheme 1) are readily obtained from the corresponding glycal derivatives **1** upon treatment with various alcohols, generally in the presence of a Lewis acid catalyst. This reaction was discovered by Ferrier in 1969 by using $BF_3 \cdot Et_2O$ as a Lewis acid catalyst and is popularly known as the Ferrier reaction.[7] Apart from $BF_3 \cdot Et_2O$,[7,8] a large number of other Lewis acid catalysts have been reported to effect the Ferrier reaction, which include $InCl_3$,[9] $SnCl_4$,[10] $Yb(OTf)_3$,[11] $Sc(OTf)_3$,[12] $FeCl_3$,[13] $BiCl_3$,[14] $ZnCl_2$,[15] $LiBF_4$,[16] montmorillionite K-10,[17] $Dy(OTf)_3$,[18] and $ZrCl_4$.[19] In addition to these Lewis acids, oxidants such as DDQ,[20] NIS,[21] I_2,[22] $I(Coll)_2\ ClO_4$,[23] and CAN[24] have also been employed for the Ferrier reaction.

SCHEME 1



Recently, an interesting reagent system, viz., $HClO_4$ supported on silica gel, has been introduced[25] for converting alcohols to the corresponding acetates in an effective manner. Glycals are known to react with alcohols in the presence of protic acid catalysts such as $MeOH \cdot HCl$,[26] cationic-exchange resin AG 50WX$_2$,[27] and Ph_3P/HBr[28] to form the corresponding 2-deoxy-*O*-glycosides. It was therefore of interest to us to find out the behavior of the reagent system of $HClO_4$ supported on silica gel, which is cheap and moisture-insensitive, toward glycals in the presence of alcohols. In this Note we wish to report that $HClO_4$ supported on column silica gel (200−400 mesh)[29] allows the reaction of several alcohols, including primary, secondary, and allylic alcohols, phenols, and thiophenol with 3,4,6-tri-*O*-acetyl-D-glucal **1** to yield the corresponding 2,3-unsaturated-*O*-glycosides in good to excellent yields and in short reaction times with high α selectivity. Further, it does not require any workup, as mere filtration of the catalyst followed by chromatographic purification is sufficient. Our results are summarized in Table 1. All reactions were completed in less than 1 h except with MeOH, EtOH, and cholesterol. Varying amounts of

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[17] (a) Toshima, K.; Ishizuka, T.; Matsuo, G.; Nakata, M. *Synlett* **1995**, 306. (b) Shanmugasundaram, B.; Bose, A. K.; Balasubramanian, K. K. *Tetrahedron Lett.* **2002**, *43*, 6795. (c) de Oliviera, R. N.; de Freitas, J. R.; Srivastava, R. M. *Tetrahedron Lett.* **2002**, *43*, 2141.

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[21] Fraser-Reid, B.; Madsen, R. *J. Org. Chem.* **1995**, *60*, 3851.

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[24] Yadav, J. S.; Reddy, B. V. S.; Pandey, S. K. *New J. Chem.* **2001**, *25*, 538.

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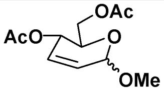
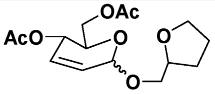
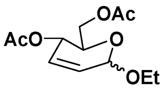
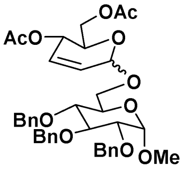
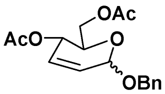
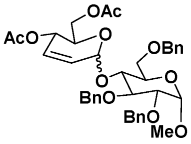
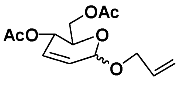
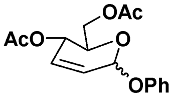
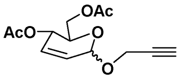
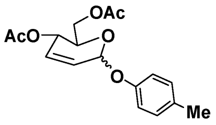
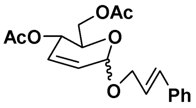
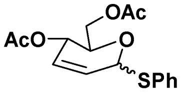
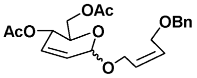
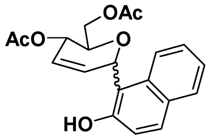
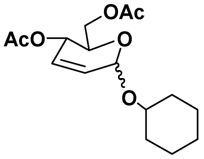
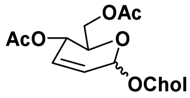
[29] $HClO_4$ supported on silica gel was prepared as follows: 105.3 mg of $HClO_4$ (0.125 mmol, as a 70% aqueous solution) was added to the suspension of silica gel (2 g, 200−400 mesh) in Et_2O. The mixture was concentrated, and the residue was heated at 100 °C for 6 h to get $HClO_4-SiO_2$ as a free flowing powder. The loading capacity of $HClO_4$ on silica gel is 0.37 mmol H^+/g. We thank the editor and the referee for suggesting that we determine the loading capacity of $HClO_4$ in this reagent system.

10.1021/jo049415j CCC: $27.50

TABLE 1. Ferrier Reaction of 2,3-Tri-*O*-acetyl-D-glucal with Alcohols in the Presence of the $HClO_4-SiO_2$ Reagent System

Entry	Product	Time (min)	yield (%)	α:β	Entry	Product	Time (min)	yield (%)	α:β
1		180[a]	82	6:1[7c]	10		45[b]	84	7:2[12]
2		180[a]	81	15:1[7c]	11		5[c]	86	7:2[31]
3		20[b]	82	6:1[18]	12		10[d]	65	α[31]
4		30[a]	81	8:1[18]	13		5[c]	54	α[18]
5		20[b]	92	5:1[18]	14		10[c]	70	11:1[17b]
6		30[b]	82	8:1[12]	15		20[c]	60	20:1[32]
7		20[b]	95	6:1[12]	16		20[c]	73	5:1
8		45[b]	92	24:1[30]					
9		150[b]	86	23:1[14]					

[a] 300 mg. [b] 100 mg. [c] 5 mg. [d] 20 mg of $HClO_4-SiO_2$ used per 100 mg of tri-*O*-acetyl-D-glucal **1**.

$HClO_4-SiO_2$ reagent system were needed for better yields and shorter reaction time, depending on the glycosyl acceptors. Thus, with phenols, thiophenol, methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside, and methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside, the reactions were completed within less than 20 min, requiring only 5−20 mg of the reagent per 100 mg of glucal **1**. On the other hand, reactions with aliphatic alcohols required 100−300 mg of the reagent per 100 mg of the glucal and also required longer reaction time to obtain better yields. Further, anomeric stereocontrol was found to be particularly high in reactions using cyclohexanol (entry 8), cholesterol (entry 9), 4-unprotected sugar (entry 12), phenol (entry 13), and thiophenol (entry 15). Interestingly, in the reaction with β-naphthol, the corresponding 1-*C*-glucoside was formed, presumably via rearrangement[33] of the corresponding *O*-glucoside. Formation of the *C*-glucoside was confirmed by its acetylation followed by the characterization of the corresponding acetylated

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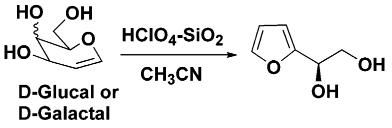
(31) Takeda, K.; Nakamura, H.; Ayabe, A.; Akiyama, A.; Harigaya, Y.; Mizuno, Y. *Tetrahedron Lett.* **1994**, *35*, 125.

(32) Raadt, A. D.; Ferrier, R. J. *Carbohydr. Res.* **1991**, *216*, 93.

SCHEME 2

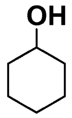
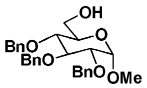
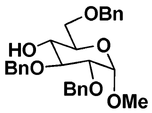
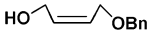


3 **4**

product by ^{1}H NMR, ^{13}C NMR, IR, and mass spectral data. Unfortunately, however, reaction of glucal **1** with *tert*-butyl alcohol did not give a clean product. Apart from the fact that the $HClO_4-SiO_2$ reagent system is cheaper than many catalysts used for the Ferrier reaction, in some respects such as % yield of the product, time required for the reaction, or the anomeric selectivity, the present method is also better than some of the known methods, as can be gauged from the data presented in Table 2. We therefore hope that the Ferrier reaction using the $HClO_4-SiO_2$ reagent system will be useful in organic synthesis.

Furanoid skeletons are important components[34] of many biologically important natural products. Besides this, an optically active furan derivative such as a furan diol **4** (Scheme 2) is well recognized[35] as a useful chiral building block in organic synthesis. Gonzalez et al.[36] reported the transformation of D-glucal **3** to furan diol **4** (Scheme 2) using $HgSO_4$ in the presence of concentrated sulfuric acid–dioxane solution. Subsequently, Hayashi et al.[37] screened several catalysts such as $Pd(OAc)_2$, $RuCl_2(PPh_3)$, $Sm(OTf)_3$, and $Yb(OTf)_3$ for this transformation and reported the formation of diol **4** in yields ranging from 44% to 70% and requiring 30–165 min at 80–100 °C. However, some of these catalysts are expensive, $HgSO_4$ is toxic in nature, and yield of the diol **4** is not very good in some of these reactions. In view of this, recently $InCl_3{\cdot}3H_2O$ has been introduced[38] as a catalyst for this transformation, which requires 10 mol % of it for the reaction to be completed in 2.5 h, giving diol **4** in 82% yield from D-glucal. We have now found that the present reagent system, viz., $HClO_4$-supported silica gel (5 wt %), reacts with D-glucal to form the diol **4** in 89% yield. Likewise, D-galactal also readily reacted with this reagent forming the diol **4** in 82% yield, although it required a bit longer time (2.5 h) at 80 °C. The diol **4** obtained from both D-glucal as well as D-galactal had comparable rotation value $\{[\alpha]_D = +36.0$ (c 1.0, chloroform); lit.[36] $[\alpha]_D = +38.0$ (c 3.3, chloroform)$\}$ and spectroscopic data as reported for it in the literature.[36]

TABLE 2. Comparison of Results of the Ferrier Reaction with Other Catalysts

Alcohol	Lewis acid Catalyst	Time	%Yield (α:β)
	$Sc(OTf)_3$	3 h	83 (7:1)
	$InCl_3$	10 min	90 (9:1)
	$BF_3{:}Et_2O$[a]	45 min	70 (9:1)
	Yb(OTf)	18 h	89 (11:1)
	CAN[b]	4.5 h	80 (14:1)
	$HClO_4$-SiO_2	45 min	92 (24:1)
Cholesterol	$BiCl_3$	2 h	90 (4:1)
	$FeCl_3$[c]	1 h	90 (85:15)
	CAN[b]	5 h	78 (10:1)
	$HClO_4$-SiO_2	2.5 h	86 (23:1)
	$Yb(OTf)_3$	18 h	89 (α)
	$HClO_4$-SiO_2	10 min	86 (7:2)
	$Yb(OTf)_3$	26 h	84 (α)
	$HClO_4$-SiO_2	10 min	65 (α)
PhOH	$Yb(OTf)_3$	2 h	71 (4:1)
	$Dy(OTf)_3$	1.5 h	89 (10:1)
	I_2	4 h	65 (10:1)
	$HClO_4$-SiO_2	5 min	54 (α)
PhSH	$Yb(OTf)_3$	4 h	78 (8:1)
	$BiCl_3$	1.5 h	95 (10:1)
	$HClO_4$-SiO_2	20 min	60 (20:1)
	CAN[b]	4 h	87 (4:1)
	$Sc(OTf)_3$	2 h	90 (6:1)
	$HClO_4$-SiO_2	20 min	95 (6:1)

[a] 0 °C to room temperature. [b] Refluxing in acetonitrile. [c] 85 °C in toluene.

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(33) (a) Matsumoto, T.; Yamaguchi, H.; Suzuki, K. *Tetrahedron* **1997**, *53*, 16533. (b) Booma, C.; Balasubramanian, K. K. *Tetrahedron Lett.* **1992**, *33*, 3049. (c) Matsumoto, T.; Hosoya, T.; Suzuki, K. *Synlett* **1991**, 709. (d) Kometani, T.; Kondo, H.; Fujimori, Y. *Synthesis* **1988**, 1005.

(34) (a) Westley, J. W. *Polyether Antibiotics: Naturally Occurring Acid Ionophores*; Marcel Dekker: New York, 1982; Vols.1 and 2. (b) Hanessian, S. *Acc. Chem. Res.* **1979**, *12*, 159.

(35) (a) Babu, R. S.; Zhou, M.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2004**, *126*, 3428 (b) Saeed, M.; Ilg, T.; Schick, M.; Abbas, M.; Voelter, W. *Tetrahedron Lett.* **2001**, *47*, 7401. (c) Harris, J. M.; Keränen, M. D.; Nguyen, H.; Young, V. G.; O'Doherty, G. A. *Carbohydr. Res.* **2000**, *328*, 17.

(36) Gonzalez, F.; Lesage, S.; Perlin, A. S. *Carbohydr. Res.* **1975**, *42*, 267.

(37) Hayashi, M.; Kawabata, H.; Yamada, K. *Chem. Commun.* **1999**, 965.

(38) Babu, B. S.; Balasubramanian, K. K. *J. Org. Chem.* **2000**, *65*, 4198.

During these reactions, there appears to be some racemization and the diol obtained from D-glucal was 85% enantiomerically pure,[39] whereas the one obtained from D-galactal was 87% enantiomerically pure. Among all of the reagents reported so far, for the above transformation, vide supra, the present reagent, viz., $HClO_4$ supported on silica gel, clearly is the best for this purpose from every angle i.e., the cost, easy availability, yield of the product, and the reaction time. In these transformations also, the workup merely required filtration of the catalyst followed by purification.

In conclusion, we believe that the reagent system $HClO_4$ supported on silica gel is useful for carrying out Ferrier reactions leading to 2,3-unsaturated-*O*-glucosides **2** and obtaining the chiral furan diol **4**. We expect that these methods will find application in organic synthesis, as this reagent system is nontoxic, inexpensive, and environmentally acceptable.

Experimental Section

Genera1 Procedure for 2,3-Unsaturated-*O*-glycosides Preparation. To a stirred mixture of tri-*O*-acetyl-D-glucal (100 mg, 0.37 mmol) and an alcohol (1 equiv; 2 equiv in case of MeOH, EtOH, and allyl alcohol) in dichloromethane (1 mL) was added $HClO_4-SiO_2$ (amount as indicated in Table 1) at ambient temperature. The mixture was stirred for appropriate time (Table 1), and completion of the reaction was monitored by TLC analysis. The reaction mixture was then filtered and washed with dichloromethane, and the combined organic extract was concentrated under vacuum. All the products were purified by silica gel column chromatography.

1-*C*-Glucoside (Corresponding to Entry 16). ^{1}H NMR (400 MHz, $CDCl_3$) (α-anomer) δ: 2.13 (s, 3H), 2.15 (s, 3H), 4.08−4.11 (dt, J = 2.92, 5.84, 9.28 Hz, 1H), 4.32−4.39 (m, 2H), 5.65 (dd, J = 1.96, 9.28 Hz, 1H), 5.87−5.90 (m, 1H), 5.97−6.00 (dd, 1H, J = 4.4, 11.84 Hz), 6.31 (brs, 1H), 7.09−7.79 (m, 6H), 8.53 (s, 1H). (β-anomer) δ: 8.34 (s, 1H), 6.11(brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) (α-anomer) δ: 20.7, 20.9, 62.4, 64.2, 75.3, 75.3, 119.9, 120.6, 112.6−154.0 (10 aromatic carbons), 170.1, 170.8. IR(CH_2Cl_2) ν: 3362, 1742, 1622 1264, 1230 cm^{-1}. MSES$^+$: 379 $[M + Na]^+$, 295 $[(M + 2) - 86 + Na]^+$, 237 $[M - 143 + Na]^+$.

Spectral Data for the Acetate of 1-*C*-Glucoside. ^{1}H NMR (400 MHz, $CDCl_3$) (α-anomer) δ: 2.06 (s, 3H), 2.14 (s, 3H), 2.38 (s, 3H), 4.06−4.12 (m, 1H), 4.21−4.34 (m, 2H), 5.67−5.69 (m, 1H), 5.89−6.02 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) (α-anomer) δ: 20.8, 21.0, 21.1, 63.5, 65.2, 71.6, 75.4, 121.4−146.7 (10 aromatic and 2 olefinic carbons), 169.6, 170.4, 171.0. IR (CH_2Cl_2) ν: 3055, 1740, 1232, 739 cm^{-1}. MSES$^+$: 819 $[2M + Na]^+$, 421 $[M + Na]^+$.

Preparation of Furan-diol 4. The $HClO_4-SiO_2$ reagent system (5 wt %) was added to a solution of D-glycal in acetonitrile at room temperature. Stirring was continued for 1 h with D-glucal, whereas with D-galactal the reaction mixture was heated at 80 °C for 2.5 h. After completion of the reaction (monitored by TLC), the reaction mixture was filtered, and the filtrate was concentrated and purified by column chromatography. The spectral data was in accordance with the reported data.[36]

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds corresponding to entry 16 (Table 1), the corresponding acetate, and chiral furan diol 4. This material is available free of charge via the Internet at http://pubs.acs.org.

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(39) We thank one of the referees for suggesting that we determine the extent of racemization in these reactions, which was determined from the ^{1}H NMR spectral data of the Mosher ester of diol **4**. It was also further confirmed from the shift reagent [(+)-Eu(hfc)$_3$]-based studies of the ^{1}H NMR spectral data of the diacetate of diol **4**.