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Note

Synthesis of 2,3-unsaturated *C*-glycosides by $HClO_4$–SiO_2 catalyzed Ferrier rearrangement of glycals☆

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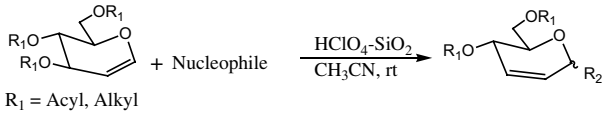
Abstract—Alkyl 2,3-unsaturated *C*-glycopyranosides have been prepared by Ferrier rearrangement of acyl or alkyl protected glycals catalyzed by $HClO_4$–SiO_2.

Keywords: Ferrier reaction; Glycals; 2,3-Dideoxy *C*-glycosides; $HClO_4$–SiO_2

2,3-Unsaturated glycosides or 'pseudoglycals' obtained by Ferrier rearrangement of glycals are versatile chiral intermediates in the synthesis of modified carbohydrates and nucleosides with important pharmacological properties.[1–5] This class of compound can be transformed into 2-deoxy and 2,3-dideoxy sugars, which are building blocks for the total synthesis of many antibiotics.[6–11] *C*-Glycosides are potential inhibitors of several glycosyltransferases and glycosidases and are hydrolytically stable analogs of glycans involved in many important intra- and intercellular processes.[12] Classically, 2,3-unsaturated *C*-glycosides are prepared by Ferrier rearrangement of acyloxy glycals catalyzed by strong Lewis acids (e.g., boron trifluoride diethyl etherate, titanium tetrachloride).[13–15] Due to its great significance in carbohydrate chemistry, there has been a growing interest in identifying new catalysts for the Ferrier reaction. The use of a number of reagents for this transformation has appeared in the recent literature, including indium chloride,[16,17] indium bromide,[18] acidic montmorillonite K 10,[19] DDQ,[20] trimethylsilyltriflate,[21] and trichloroacetimidate.[22] Recently, Lewis acid catalyzed Ferrier reaction has been exploited to generate β-selective *C*-disaccharides.[23] Despite their usefulness, many of the abovementioned methods suffer from disadvantages such as strong acidity (boron trifluoride diethyl etherate, titanium tetrachloride and montmorillonite K 10) strong oxidizing conditions (DDQ), long reaction times, unsatisfactory yields, low stereoselectivity, the requirement for an excess of promoter (boron trifluoride diethyl etherate), or high cost (TMSOTf). Therefore, there is a need for a Ferrier rearrangement protocol that employs an inexpensive and mild catalyst, ideally the one that is more environmental friendly than those currently in use.

We set out to explore the potential of $HClO_4$–SiO_2, an inexpensive catalyst for the preparation of 2,3-unsaturated *C*-glycosides through Ferrier rearrangement of glycals. Reported here are our studies on the $HClO_4$–SiO_2 catalyzed allylic rearrangement of acylated and alkylated glycals with silylated *C*-nucleophiles and active methylene compounds (Scheme 1). The reaction proceeds smoothly at room temperature producing excellent yield of 2,3-unsaturated *C*-glycosides without formation of any byproducts.



R_1 = Acyl, Alkyl

Scheme 1.

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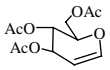
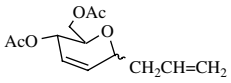
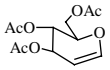
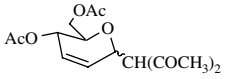
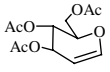
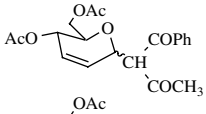
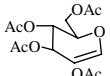
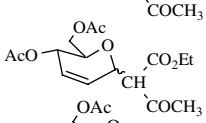
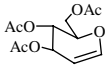
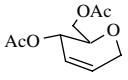
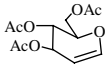
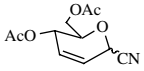
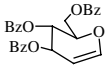
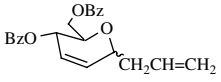
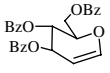
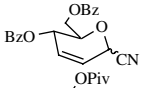
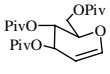
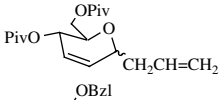
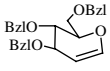
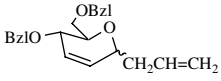
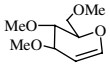
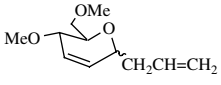
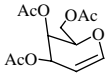
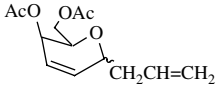
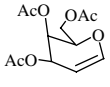
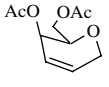
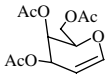
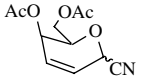
Triflate salts release triflic acid, which catalyze the allylic rearrangement of acylated or alkylated glycals leading to the Ferrier rearrangement product. As a cheaper alternative, we have chosen $HClO_4$, the strongest mineral acid able to catalyze this transformation. To avoid the presence of water in the reaction medium, which has a deleterious effect in the formation of the product, $HClO_4$ has been impregnated on silica gel. The $HClO_4$–SiO_2 acted as an insoluble promoter, which could be removed from the reaction mixture by simple filtration. The promoter system is a non-corrosive free flowing powder that can be stored at room temperature for several months without loosing its catalytic potentiality. Although $HClO_4$–acetic anhydride mixtures are known to explode, in our case no such event was witnessed when using $HClO_4$–SiO_2. Recently $HClO_4$–SiO_2 has been used to catalyze acetylation of alcohols and phenols using acetic acid.[24]

In a first set of experiments, 3,4,6-tri-*O*-acetyl-D-glucal was treated with allyl trimethylsilane (1.2 equiv) in acetonitrile by varying the quantity of catalyst and reaction temperature. After some experimentation, it was found that the use of 50 mg of $HClO_4$–SiO_2 catalyst per mmol of the protected glycal produced the corresponding 4,6-di-*O*-acetyl-2,3-unsaturated *C*-allyl glycosides in excellent yield within a few minutes at room temperature (Table 1). Using the same conditions, a ser-

Table 1. $HClO_4$–SiO_2 promoted Ferrier rearrangement of glycals leading to 2,3-unsaturated *C*-glycosides

Entry	Glycals (**1**)	Acceptors (**2**)	Products (**3**)[a]	Time (min)	Yield (%)[b]	α:β	Ref.
a		$TMSCH_2$–CH=CH_2		25	90	20:1	18
b		$(CH_3CO)_2CH_2$		60	75	1.5:1	—
c		$PhCOCH_2COCH_3$		60	70	6:1	—
d		$CH_3COCH_2CO_2Et$		60	65	2.5:1	—
e		Et_3SiH		20	85	—	25
f		Me_3SiCN		20	62	2:1	18
g		$TMSCH_2$–CH=CH_2		20	80	10:1	18
h		Me_3SiCN		20	70	3:1	18
i		$TMSCH_2$–CH=CH_2		25	85	10:1	18
j		$TMSCH_2$–CH=CH_2		20	75	11:1	18
k		$TMSCH_2$–CH=CH_2		20	75	21:1	18
l		$TMSCH_2$–CH=CH_2		25	90	10:1	18
m		Et_3SiH		20	85	—	26
n		Me_3SiCN		20	70	2:1	18

[a] Products of all known compounds gave ^1H NMR and ^{13}C NMR spectra that matched data reported in the cited references. New compounds were characterized as outlined in the experimental section.

[b] Isolated yield.

ies of *C*-glycosides was prepared in excellent yield at room temperature by using 1,3-diones, β-ketoester and trimethylsilylated *C*-nucleophiles. Glycals having alkyl protecting groups (R_1 = methyl, benzyl; Scheme 1) also gave 2,3-unsaturated *C*-glycosides under these conditions without formation of any 2-deoxy glycosides. Based on the success of the *C*-glycosylation with allyltrimethylsilane, the reaction of 3,4,6-tri-*O*-acetyl-D-glucal with allyltributyltin under the same conditions was explored. However, at room temperature no reaction was observed after 12 h and heating the reaction mixture at reflux led only to about 10% of the intended product (α/β = 1:1) together with extensive decomposition.

In most of the cases, an α/β mixture of 2,3-unsaturated glycosides was obtained. Although the α- and β-isomers were inseparable by column chromatography, the ratios of the two isomers could be determined by integration of the signals in the NMR spectra of the products. The ratio of both isomers was further confirmed by HPLC and GC analysis. The α-configuration of the major product was confirmed by the positions of the anomeric protons and carbons in the ^{1}H NMR and ^{13}C NMR spectra. For further confirmation, NOE experiments were carried out, in which a considerable NOE was observed between H-1 and H-4 in all glucal derived products; however, no such enhancements were observed between H-1 and H-4 of galactal-derived products. From the NOE experiments, it is clear that for the glucal-derived products, H-1 and H-4 are in the same side of the molecule, and for the galactal-derived products, H-1 and H-4 are on the opposite side of the molecule. This data is consistent with products of the α-stereochemistry.

The present method of $HClO_4$–SiO_2 promoted Ferrier rearrangement of *O*-acylated and *O*-alkylated glycals provides an efficient protocol to prepare 2,3-unsaturated *C*-glycosides. There are several advantages in the use of $HClO_4$–SiO_2 as catalyst for this transformation, which include high yields of products, simplicity in operation, cleaner reaction profiles, short reaction times, and exceptionally high selectivity. In addition, this method does not require any additive or stringent reaction conditions. There is no need to take any special precautions in either handling the catalyst or in excluding moisture from the reaction medium.

1. Experimental

1.1. General methods

All the reactions were monitored by thin layer chromatography on silica gel coated TLC plates. The spots on TLC were visualized by warming ceric sulfate (2% $Ce(SO_4)_2$ in 2 N H_2SO_4) sprayed plates on a hot plate or in an oven at about 100 °C. Silica gel (230–400 mesh) was used for column chromatography. FAB mass spectra were recorded on JEOL SX 102/DA-6000 mass using Argon/Xenon (6 KV, 10 MA). GC experiments were performed on a Perkin–Elmer auto system using OV-225 column and dry N_2 as carrier gas. HPLC experiments were run on an analytical HPLC (Agilent 1100 series) by using C_{18} LichroCART®-250-4 column (4.6 × 150 mm) under a gradient of 10–100% CH_3CN–water with a flow rate of 1.0 mL/min at 220/254 UV absorbance. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Advance DPX 200 MHz using TMS as the internal reference. Chemical shifts are expressed in ppm. Elemental analysis was carried out on Carlo ERBA-1108 analyzer. Optical rotations were measured at 25 °C on a Rudolf Autopol III polarimeter. Commercially available grades of organic solvents were used in the reactions.

1.2. Preparation of the $HClO_4$–SiO_2 catalyst[24]

$HClO_4$ (1.8 g, 12.5 mmol, as a 70% aq solution) was added to a suspension of SiO_2 (230–400 mesh, 23.7 g) in Et_2O (70.0 mL). The mixture was concentrated and the residue was heated at 100 °C for 72 h under vacuum to furnish $HClO_4$–SiO_2 (0.5 mmol/g) as a free flowing powder (50 mg = 0.025 mmol of $HClO_4$). **Caution**: Although no explosions were reported under these conditions, extreme care has to be applied for large-scale reactions. The generation of the catalyst should be performed with special care and in a safe environment.

1.3. Typical experimental protocol

To a solution of tri-*O*-acetyl-D-glucal (272 mg, 1.0 mmol) and allyltrimethylsilane (1.2 mmol) in CH_3CN (3.0 mL) was added $HClO_4$–SiO_2 (50.0 mg) and the reaction mixture was stirred at room temperature for an appropriate time (see Table 1). The reaction mixture was then filtered through a Celite bed and concentrated to dryness under reduced pressure. The crude reaction mixture was purified over SiO_2 using hexane–EtOAc as the eluant to furnish the desired 2,3-unsaturated *C*-glycoside. Following the same reaction conditions, other *C*-nucleophiles gave the corresponding *C*-glycosides as summarized in Table 1. Products of all known compounds gave NMR spectra that matched data reported in the cited references. New compounds are characterized according to identity and purity. Spectral data of products that are not reported are listed below.

1.4. 3-*C*-(4,6-Di-*O*-acetyl-2,3-dideoxy-*erythro*-hex-2-eno-α-D-pyranosyl)-2,4-pentanedione (3b)

Yellow oil; R_f (1:4, EtOAc–hexane) 0.65; $[\alpha]_D^{25}$ +96.3 (*c* 1.0, $CHCl_3$); ν_{max} (liquid film) 3432–3020 (br), 1727, 1372, 1250, 1046, 758, 607 cm^{-1}; ^{1}H NMR

(200 MHz, $CDCl_3$): δ_H 5.86–5.80 (2H, m, H-2, H-3), 5.24–5.22 (1H, m, H-4), 4.85–4.80 (1H, m, H-5), 4.16–4.13 (2H, m, H-$6_{a,b}$), 3.86–3.82 (1H, m), 3.80–3.67 (1H, m), 2.25, 2.22, 2.08, 2.06 (12H, 4s, 4COCH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 201.6, 201.2, 170.9, 170.5, 130.3, 126.2, 72.3, 71.0, 70.6, 64.8, 62.8, 31.0, 28.3, 21.3, 21.0; MS (FAB): *m/z* 313 $[M+1]^+$, 253 $[M-CO_2CH_3]^+$, 238 $[M-CO_2CH_3-CH_3]^+$, 213 $[C_{10}H_{13}O_5]^+$, 153 $[C_8H_9O_3]^+$, 111 $[C_6H_7O_2]^+$. Anal. Calcd for $C_{15}H_{20}O_7$ (312): C, 57.69; H, 6.45. Found: C, 57.76; H, 6.55.

1.5. 2-*C*-(4,6-Di-*O*-acetyl-2,3-dideoxy-*erythro*-hex-2-eno-α-D-pyranosyl)-1-phenyl-1,3-butanedione (3c)

Yellow oil; R_f (1:4, EtOAc–hexane) 0.75; $[\alpha]_D^{25}$ +45.6 (*c* 1.0, $CHCl_3$); ν_{max} (liquid film) 3024, 2372, 1739, 1676, 1370, 1222, 1048, 766, 669 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 8.02–7.45 (5H, m, aromatic), 5.91–5.76 (2H, m, H-2, H-3), 5.30–5.23 (1H, dd, *J* 10.5, 1.5 Hz, H-1), 5.19–5.15 (1H, dd, *J* 7.2, 1.0 Hz, H-4), 4.83 (1H, d, *J* 10.5 Hz, H-1′), 3.97–3.90 (1H, m, H-5), 2.24 (3H, s, CH_3), 2.11, 2.07 (6H, 2s, 2COCH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 201.5, 194.8, 171.1, 170.6, 130.7, 129.3, 128.1 (3C), 127.1 (2C), 126.1, 74.9, 74.7, 66.3, 65.0, 62.8, 27.1, 21.3, 21.0; MS (FAB): *m/z* 375 $[M+1]^+$, 359 $[M-CH_3]^+$, 331 $[M-COCH_3]^+$, 315 $[M-OCOCH_3]^+$, 297 $[M-C_6H_5]^+$, 269 $[M-COC_6H_5]^+$, 255 $[M-CH_2COPh]^+$, 213 $[C_{10}H_{13}O_5]^+$, 153 $[C_8H_9O_3]^+$, 111 $[C_6H_7O_2]^+$. Anal. Calcd for $C_{20}H_{22}O_7$(374): C, 64.16; H, 5.92. Found: C, 64.07; H, 6.03.

1.6. 2-*C*-(4,6-Di-*O*-acetyl-2,3-dideoxy-*erythro*-hex-2-eno-α-D-pyranosyl)ethyl-3-keto-butanoate (3d)

Yellow oil; R_f (1:4, EtOAc–hexane) 0.55; $[\alpha]_D^{25}$ +12.3 (*c* 1.0, $CHCl_3$); ν_{max} (liquid film) 2984, 236, 1742, 1371, 1235, 1043, 759 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H, 6.07–6.06 (1H, dd, *J* 1.5, 0.9 Hz, H-2), 6.05–6.01 (1H, dd, *J* 1.8, 0.6 Hz, H-3), 5.89–5.85 (1H, m, H-1), 5.17–5.12 (1H, m, H-4), 4.30–4.10 (3H, m, H-5, OCH_2CH$_3$), 3.95–3.86 (2H, m, H-$6_{a,b}$), 3.77 (1H, d, *J* 10 Hz, H-1′), 2.31 (3H, s, CH_3), 2.08 (6H, s, 2COCH_3), 1.30 (3H, t, *J* 5.7 Hz, CH$_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 201.6, 171.1, 170.6, 167.0, 130.4, 125.8, 70.7, 70.5, 63.6, 63.4, 62.1, 61.9, 21.2, 21.0, 14.3 (2C); MS(FAB): *m/z* 343 $[M+1]^+$, 313 $[M-CH_2CH_3]^+$, 299 $[M-COCH_3]^+$, 283 $[M-CO_2CH_3]^+$, 240 $[M-CO_2CH_3-COCH_3]^+$, 213 $[C_{10}H_{13}O_5]^+$, 153 $[C_8H_9O_3]^+$, 111 $[C_6H_7O_2]^+$. Anal. Calcd for $C_{16}H_{22}O_8$ (342): C, 56.13; H, 6.48. Found: C, 56.02; H, 6.56.

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References

1. Schmidt, R. R.; Angerbauer, R. *Carbohydr. Res.* **1979**, *72*, 272–275.
2. Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380–1419.
3. Fraser-Reid, B. *Acc. Chem. Res.* **1985**, *18*, 347–354.
4. Bussolo, V. D.; Kim, Y.-J.; Gin, D. Y. *J. Am. Chem. Soc.* **1998**, *120*, 13515–13516.
5. Srivastava, R. M.; Oliveira, F. J. S.; Silva, L. P.; de Freitas Filho, J. R.; Oliveira, S. P.; Lima, V. L. M. *Carbohydr. Res.* **2001**, *332*, 335–340.
6. Holder, N. *Chem. Rev.* **1982**, *82*, 287–332.
7. Liu, Z. J.; Zhou, M.; Min, J. M.; Zhang, L. H. *Tetrahedron: Asymmetry* **1999**, *10*, 2119–2127.
8. Brito, T. M. B.; Silva, L. P.; Siqueira, V. L.; Srivastava, R. M. *J. Carbohydr. Chem.* **1999**, *18*, 609–616.
9. Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976–4978.
10. Paterson, L.; Keown, L. E. *Tetrahedron Lett.* **1997**, *38*, 5727–5730.
11. Horita, K.; Sakurai, Y.; Nagasawa, M.; Hachiya, S.; Tonemistu, O. *Synlett* **1994**, 43–45.
12. Weatherman, R. V.; Mortell, K. H.; Chervenak, M.; Kiessling, L. L.; Toone, E. J. *Biochemistry* **1996**, *35*, 3619–3624.
13. Ferrier, R. J.; Prasad, N. *J. Chem. Soc. (C)* **1969**, 570–574.
14. Ferrier, R. J. *Topics Curr. Chem.* **2001**, *215*, 153–175.
15. Danishefsky, S.; Keerwin, J. F. *J. Org. Chem.* **1982**, *47*, 3803–3805.
16. Babu, B. S.; Balasubramanian, K. K. *Tetrahedron Lett.* **2000**, *41*, 1271–1274.
17. Das, S. K.; Reddy, K. A.; Roy, J. *Synlett* **2003**, 1607–1610.
18. Yadav, J. S.; Reddy, B. V. S. *Synthesis* **2002**, 511–514.
19. Toshima, K.; Miyamoto, N.; Matsuo, G.; Nakata, M.; Matsumara, S. *J. Chem. Soc., Chem. Commun.* **1996**, 1379–1380.
20. Toshima, K.; Ishizuka, T.; Matsuo, G.; Nakata, M. *Chem. Lett.* **1993**, 2013–2016.
21. Dawe, R. D.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1981**, 1180–1181.
22. Schmidt, R. R.; Hoffman, M. *Tetrahedron Lett.* **1982**, *23*, 409–412.
23. Gemmell, N.; Meo, P.; Osborn, H. M. I. *Org. Lett.* **2003**, *5*, 1649–1652.
24. Chakraborti, A. K.; Gulhane, R. *Chem. Commun.* **2003**, 1896–1897.
25. Nicolaou, K. C.; Hwang, C. K.; Marron, B. E.; DeFrees, S. A.; Couladouros, E. A.; Abe, Y.; Carroll, P. J.; Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 3040–3054.
26. Crimmins, M. T.; King, B. W.; Zuercher, W. J.; Choy, A. L. *J. Org. Chem.* **2000**, *65*, 8499–8509.