Tetrahedron Letters 55 (2014) 5813–5816

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

$Y(OTf)_3$ as a highly efficient catalyst in Ferrier Rearrangement for the synthesis of *O*- and *S*-2,3-unsaturated glycopyranosides

Peiran Chen [a,b,*], Shan Li [a]

[a] Key Lab of Eco-Textile, The Ministry of Education, Donghua University, 2999 Renmin Road North, Songjiang District, Shanghai 201620, China
[b] Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, CAS, Shanghai 200032, China

ARTICLE INFO

Article history:
Received 13 July 2014
Revised 13 August 2014
Accepted 22 August 2014
Available online 29 August 2014

Keywords:
$Y(OTf)_3$
3,4,6-Tri-*O*-acetyl-D-glucal
3,4,6-Tri-*O*-benzyl-D-glucal
3,4-Di-*O*-acetyl-L-rhamnal
2,3-Unsaturated glycoside
Ferrier Rearrangement

ABSTRACT

By using $Y(OTf)_3$ as the catalyst, a series of 2,3-unsaturated-glucosides have been synthesized from 3,4,6-tri-*O*-acetyl-D-glucal, 3,4-di-*O*-acetyl-L-rhamnal, and 3,4,6-tri-*O*-benzyl-D-glucal under mild reaction conditions in good yields with high anomeric selectivities. It was found that, in this reaction, 3,4,6-tri-*O*-benzyl-D-glucal behaved differently from the other two glucals when it was reacted with phenol, *O*-benzyl glucoside instead of *O*-phenyl glucoside formed as the sole product. An explanation is given for this phenomenon.

Owing to their versatile chemical transformations, alkyl and aryl 2,3-unsaturated glycosides are important chiral intermediates in the synthesis of biologically active molecules[1] and new functional materials.[2] Ferrier Rearrangement is an efficient and facile reaction for the synthesis of 2,3-unsaturated glycopyranosides.[3] A variety of reagents have been used to promote this reaction, including Bronsted acids,[4] Lewis acids,[5] as well as other reagents such as oxidants.[6] Due to their special properties and high catalytic activity, rare earth metal salts as catalyst have recently gained more and more applications. Among them, $Sc(OTf)_3$, $CeCl_3$, $Dy(OTf)_3$, $Er(OTf)_3$, and $Yb(OTf)_3$ have been employed as the catalysts in Ferrier Rearrangement.[7] In our continuing effort to search for more efficient catalyst for Ferrier Rearrangement, we found $Y(OTf)_3$ is a highly efficient catalyst for the transformation of various glucals to the *O*- and *S*-2,3-unsaturated glucosides. Here we reported our result.

First of all, reaction condition optimization was performed. Among YF_3, Y_2O_3, $Y_2(SO_4)_3$, and $Y(OTf)_3$, we found $Y(OTf)_3$ to be the most efficient. For the reaction solvent, among the tested acetonitrile, methylene dichloride, tetrahydrofuran, and toluene, acetonitrile gave the highest conversion under the catalysis of $Y(OTf)_3$. For the reaction temperature, shortest reaction time and highest yield were obtained at 40 °C. Therefore, the established reaction conditions are mild.

Under the established reaction conditions, 2,3-unsaturated glycosides were synthesized from three glycals and various nucleophiles. Hereinafter we will discuss our results based on the glycals used.

Table 1 shows the result of 3,4,6-tri-*O*-acetyl-D-glucal (**1**). We can see that when alcohols were used as nucleophile, the expected products were obtained in high yields with good anomeric selectivities. Phenols and thiols needed longer time to give good to moderate yields with high selectivities.

A report mentioned that when 3,4,6-tri-*O*-acetyl-D-glucal was treated with *p*-methoxyphenol in CH_2Cl_2 with $BF_3{\cdot}OEt_2$ as the catalyst, *C*-glycoside was obtained exclusively.[8] However, in our case, no such phenomenon occurred. Phenol, *p*-methoxyphenol, and 2-naphthol gave the normal *O*-glucoside products in good yields (entries 7–9), which can be confirmed by the two *ortho* aromatic signals in the ^1H NMR spectra of the products (**3g**, **3h**, and **3i**).

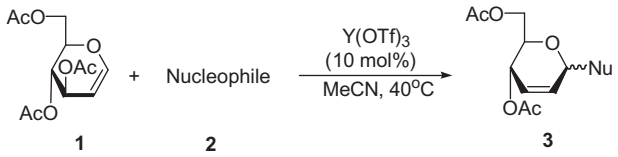
Table 2 shows the results of 3,4-di-*O*-acetyl-L-rhamnal (**4**), which appeared to be similar to the results given in Table 1. The anomeric selectivities were high but the yields were slightly lower than those of 3,4,6-tri-*O*-acetyl-D-glucal (**1**). Phenols as the nucleophile again afforded the normal *O*-glycoside products (entries 6 and 7).

Results in Table 3 show that 3,4,6-tri-*O*-benzyl-D-glucal (**6**) was less active than the former two glycals. In the case of alcohols (entries 1–4) as the nucleophiles, the reaction needed longer time

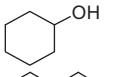
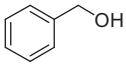
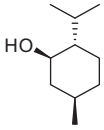
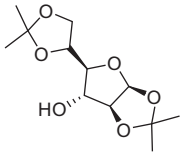
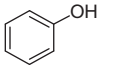
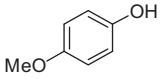
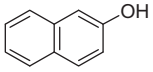
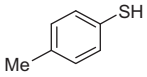
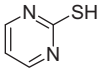
* Corresponding author. Tel.: +86 21 67792594.
E-mail address: prchen@dhu.edu.cn (P. Chen).

http://dx.doi.org/10.1016/j.tetlet.2014.08.092
0040-4039/

Table 1
$Y(OTf)_3$ catalyzed Ferrier Rearrangement of 3,4,6-tri-*O*-acetyl-D-glucal (**1**) with nucleophiles (**2**)[a]

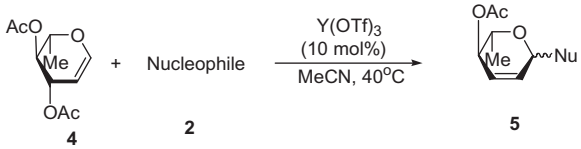


1 2 3

Entry	Nucleophile (**2**)	Reaction time (min)	Yield[b] (%)/(α:β)[c]
1	EtOH	15	**3a**: 91% (17:1)
2		18	**3b**: 90% (11:1)
3		10	**3c**: 85% (9:1)
4		8	**3d**: 77% (8:1)
5		20	**3e**: 77% (11:1)
6		20	**3f**: 82% (α only)
7		120	**3g**: 65% (α only)
8		90	**3h**: 75% (α only)
9		100	**3i**: 61% (α only)
10		30	**3j**: 82% (α only)
11		180	**3k**: 70% (α only)

[a] General reaction conditions: tri-*O*-acetyl-D-glucal (**1**) (188 mg, 0.7 mmol), nucleophile (**2**) (1.5 equiv), $Y(OTf)_3$ (10 mol %), MeCN (5 mL), 40 °C.
[b] Isolated yield.
[c] The anomeric ratio was determined by integration of the anomeric hydrogen in the ^1H NMR spectra.

Table 2
$Y(OTf)_3$ catalyzed Ferrier Rearrangement of 3,4-di-*O*-acetyl-L-rhamnal (**4**) with nucleophiles (**2**)[a]



4 2 5

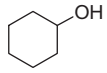
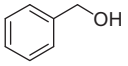
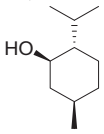
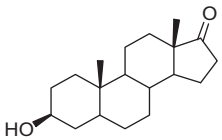
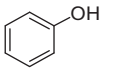
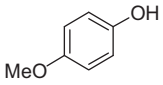
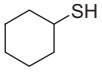
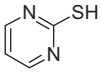
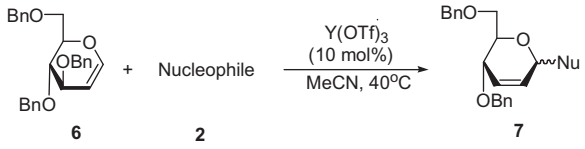
Entry	Nucleophile (**2**)	Reaction time (min)	Yield[b] (%)/(α:β)[c]
1		10	**5a**: 86% (α only)

Table 2 (*continued*)

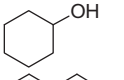
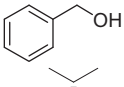
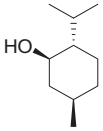
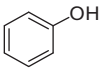
Entry	Nucleophile (**2**)	Reaction time (min)	Yield[b] (%)/(α:β)[c]
2		18	**5b**: 85% (α only)
3		10	**5c**: 81% (α only)
4		8	**5d**: 79% (α only)
5		120	**5e**: 70% (3:1)
6		120	**5f**: 75% (2.5:1)
7		90	**5g**: 75% (α only)
8		100	**5h**: 75% (21:1)

[a] General reaction conditions: 3,4-di-*O*-acetyl-L-rhamnal (**4**) (177 mg, 0.7 mmol), nucleophile (**2**) (1.5 equiv), $Y(OTf)_3$ (10 mol %), MeCN (5 mL), 40 °C.
[b] Isolated yield.
[c] The anomeric ratio was determined by integration of the anomeric hydrogen in the ^1H NMR spectra.

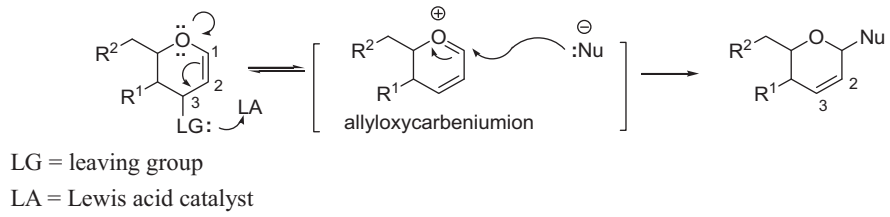
Table 3
$Y(OTf)_3$ catalyzed Ferrier Rearrangement of 3,4,6-tri-*O*-benzyl-D-glucal (**6**) with nucleophiles (**2**)[a]



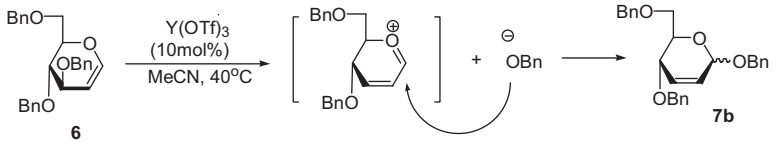
6 2 7

Entry	Nucleophile (**2**)	Reaction time (min)	Yield[b] (%)/(α:β)[c]
1		120	**7a**: 70% (10:1)
2		90	**7b**: 65% (4:1)
3		180	**7c**: 62% (α only)
4		180	**7d**: 40% (13:1)
5		48h	**7b**: 46% (8:1)

[a] General reaction conditions: 3,4,6-tri-*O*-benzyl-D-glucal (**6**) (292 mg, 0.7 mmol), nucleophile (**2**) (1.5 equiv), $Y(OTf)_3$ (10 mol %), MeCN (5 mL), 40 °C.
[b] Isolated yield.
[c] The anomeric ratio was determined by integration of the anomeric hydrogen in the ^1H NMR spectra.



Scheme 1. Mechanism of Ferrier Rearrangement proposed by Ferrier.



Scheme 2. A proposed 3,1-migration of BnO-group in 3,4,6-tri-*O*-benzyl-D-glucal promoted by $Y(OTf)_3$.

to give products in moderate yields. Moreover, when phenol was used as the nucleophile (entry 5), the reaction gave an unexpected product of *O*-benzyl glucoside (**7b**) instead of the expected *O*-phenyl glucoside in 46% yield.

Ferrier gave a mechanism[9] for his Rearrangement reaction (Scheme 1), in which, under the effect of Lewis acid, the lone pair electron moved to O—C1 bond and the electrons in C1—C2 double bond migrated to C2—C3 bond while the leaving group on C3 went to coordinate with the Lewis acid leading to the formation of an allyloxycarbenium ion, then the nucleophile attacked C1 to give the final product (Scheme 1).

To explain the phenomenon in Table 3, entry 5, we assumed the leaving group from C3 (in this case, benzyloxy anion) to be existing in free form to compete the added nucleophile (in this case, phenol). Because benzyloxy anion was much more nucleophilic than phenol, *O*-benzyl glucoside (**7b**) formed as a sole product. Treatment of 3,4,6-tri-*O*-benzyl-D-glucal (**6**) alone with $Y(OTf)_3$ under the same reaction conditions without the addition of nucleophile, we also obtained *O*-benzyl glucoside (**7b**) in 70% yield. The proposed procedure is shown in Scheme 2.

While hydron donor (such as phenol in entry 5, Table 3) presented in the reaction, the nucleophilic activity of BnO would be lowered since the formation of BnOH, which led to the relative low yield (46%) in entry 5, Table 3.

In summary, $Y(OTf)_3$ is a highly efficient catalyst for the synthesis of *O*- and *S*-2,3-unsaturated glycosides. Under our reaction conditions, 3,4,6-tri-*O*-acetyl-D-glucal and 3,4-di-*O*-acetyl-L-rhamnal afforded *O*- and *S*-products in high to good yields with high anomeric selectivities, while 3,4,6-tri-*O*-benzyl-D-glucal gave *O*-alkyl products in moderate yields with good selectivities. Interestingly, reaction of 3,4,6-tri-*O*-benzyl-D-glucal with phenol did not give the expected *O*-phenyl 2,3-unsaturated glucoside. Instead, *O*-benzyl 2,3-unsaturated glucoside was formed as the sole product.

Acknowledgments

This work is financially supported by a Grant of The National Natural Science Foundation of China (NSFC, Grant No. 21272305), The Natural Science Foundation of Shanghai Municipality (Grant No. 12ZR1400200), and The Fundamental Research Funds for the Central Universities.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.08.092.

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2. For example, see Bozell, J. J.; Tice, N. C.; Sanyal, N.; Thompson, D.; Kim, J.-M.; Vidal, S. *J. Org. Chem.* **2008**, *73*, 8763.
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