ORGANIC LETTERS

2005
Vol. 7, No. 25
5577−5579

Base-Promoted Rearrangement of Sugar Epoxides to Unsaturated Sugars

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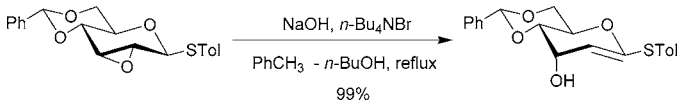
Received September 3, 2005 *(Revised Manuscript Received November 7, 2005)*

ABSTRACT



A simple and efficient method for rearranging 2,3-anhydro carbohydrates to unsaturated sugars has been developed. The exceptionally mild reaction conditions and high stereoselectivity should make this an attractive method for the preparation of unsaturated carbohydrate derivatives.

Sugar derivatives that contain double bonds are an important category of modified carbohydrate available for use in synthesis.[1] Furthermore, it has been found that some unsaturated sugar derivatives have therapeutic applications such as anti-HIV activity[2] and anti-influenza properties.[3] On the other hand, epoxides are versatile intermediates in organic synthesis. Not only are these compounds easily prepared from a variety of starting materials, but also the inherent polarity and strain of their three-membered ring makes them susceptible to reaction with a large number of reagents: electrophiles, nucleophiles, acids, bases, reducing agents, and some oxidizing agents.[4] Among these epoxide-related transformations, the rearrangement of epoxides to allylic alcohols has received considerable attention. The most well-known method to isomerize epoxides to allylic alcohols involves the use of strong and nonnucleophilic bases such as dialkylamides ($LiNR_2$).[5] In this regard, the use of chiral lithium amide bases has attracted much interest due to the great usefulness of chiral allylic alcohols in asymmetric synthesis.[6] Despite these advances, the substrates used for the base-mediated epoxide isomerization are mainly limited to aliphatic epoxides, cycloalkene oxides, organophosphorus epoxides,[7] silacyclopentene oxides,[8] and oxazolinyloxiranes.[9] Very few carbohydrate epoxides have been examined in this capacity.[10] Because of the importance of unsaturated sugars in both chemistry and pharmaceutical sciences, we became interested in exploring the possibility of forming unsaturated carbohydrates via the rearrangement of the corresponding epoxides.

First, the sugar epoxide *p*-tolyl 2,3-anhydro-4,6-*O*-benzylidene-1-thio-β-D-allopyranoside (**1**), prepared by the reaction of the 3-monosulfonate ester of *p*-tolyl 4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside **1b**[11] with sodium methoxide in

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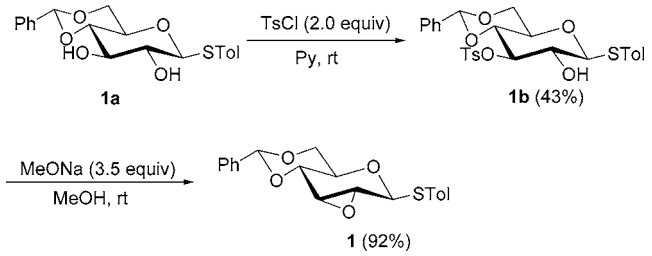
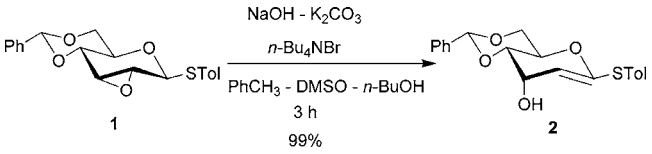
10.1021/ol052128x CCC: $30.25
Published on Web 11/15/2005

Scheme 1. Synthesis of 2,3-Anhydro β-D-Allopyranoside **1**



methanol (Scheme 1), was chosen as the substrate for rearrangement (Scheme 2). Initially, when NaOH, K_2CO_3,

Scheme 2. Base-Induced Rearrangement of Sugar Epoxide **1** to Unsaturated Sugar **2**



and tetrabutylammonium bromide were added to a solution of epoxide **1** in toluene/DMSO/*n*-butanol (V/V/V = 20/1/0.4) at room temperature, the reaction proceeded very smoothly to give the unsaturated sugar **2** in almost quantitative yield. The structure of **2** was unambiguously determined by its 1D and 2D NMR spectral analyses. When DMSO was omitted, the reaction occurred slowly. However, this drawback could be overcome by raising the reaction temperature. We also found that K_2CO_3 alone could not promote the reaction and that K_2CO_3 was not even necessary for this conversion. Thus, treatment of **1** with NaOH in toluene/*n*-BuOH at reflux in the presence of tetrabutylammonium bromide yielded, within 1 h, **2** in 99% isolated yield (Table 1, entry 1). After the success of this example, we next examined other carbohydrate epoxide substrates in the aforementioned rearrangement. All the 2,3-anhydro pyranosides were prepared by a procedure similar to that used for the preparation of **1**. As illustrated in Table 1, *p*-tolyl 2,3-anhydro-4,6-*O*-benzylidene-1-thio-β-D-mannopyranoside (**3**) reacted under the same conditions to give to a similar isomerized product **4** (82% isolated yield) (entry 2). When *p*-tolyl 2,3-anhydro-4,6-*O*-benzylidene-1-thio-β-D-gulopyranoside (**5**) was reacted under these conditions, the reaction occurred very slowly. However, the reaction speed increased after a small amount of DMF was added, and the reaction was complete within 0.5 h (entry 3). When thioglycoside **7**[12] was used as a substrate under the above-mentioned conditions, no isomerized product was detected. We therefore changed the base and solvent. Eventually, a solution of *n*-propyl 2,3-anhydro-4,6-*O*-benzylidene-1-thio-β-D-allopyranoside (**7**) in DMF was treated with *t*-BuOK at room temperature, yielding the expected product **8** in 80% isolated yield (entry 4). Likewise, the rearranged product **10** was obtained in quantitative yield from *n*-propyl 2,3-anhydro-4,6-*O*-benzylidene-1-thio-β-D-mannopyranoside (**9**) (entry 5).[13] All the substrates mentioned above were *S*-glycosides. Hence, next, we examined *O*-glycosides in this rearrangement. When a mixture of phenyl glycoside **11**,[14] *t*-BuOK, and tetrabutylammonium bromide in DMF was heated at 90 °C, a reaction did occur, and unsaturated sugar **12** was obtained in which the double bond was located between C-3 and C-4 in the carbohydrate, not between C-1 and C-2 (entry 6). When methyl glycoside **13**[15] was treated with *t*-BuOK in DMF at 80 °C, a similar result was obtained, with compound **14**[16] being in 64% isolated yield (entry 7). To further investigate the scope of the rearrangement, two furanosides were chosen as the substrates. As shown in Table 1, both *p*-tolyl 2,3-anhydro-1-thio-β-D-ribofuranoside (**15**)[17,18] and *p*-tolyl 2,3-anhydro-1-thio-α-D-lyxofuranoside (**17**)[18,19] produced the same furan derivative **16**, presumably from aromatization of the rearranged unsaturated sugar (entries 8 and 9).

The methyl glycosides **18**,[15b,c,20] **19**,[15b,21] and **20**[22] (Figure 1) were also used as the substrates to test the rearrangement.

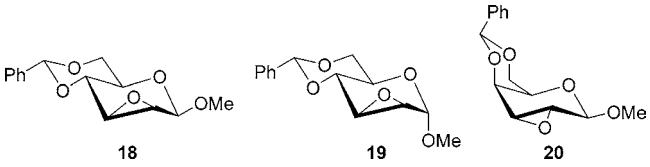


Figure 1. Epoxides incapable of rearrangement under the same conditions.

But under the above conditions, the reaction did not occur for all three epoxide reactants. On the basis of these

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(12) For the synthesis of pure compound **7**, see Supporting Information.

(13) Compounds **7** and **9** are a chromatographically inseparable mixture; therefore a mixture of **7** and **9** (ratio 1:1) was used for the rearrangement, yielding **8** and **10**. The yield of compound **10** is based on NMR analysis. See also Supporting Information.

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(15) (a) Szeja, W. *Carbohydr. Res.* **1988**, *183*, 135−139. (b) Knapp, S.; Naughton, A. B. J.; Jaramillo, C.; Pipik, B. *J. Org. Chem.* **1992**, *57*, 7328−7334. (c) Probert, M. A.; Zhang, J.; Bundle D. R. *Carbohydr. Res.* **1996**, *296*, 149−170.

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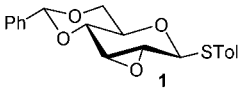
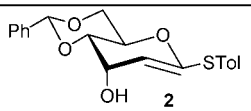
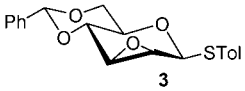
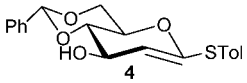
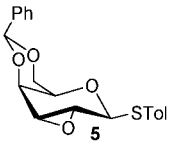
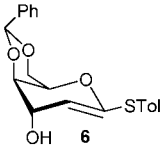
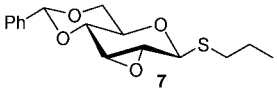
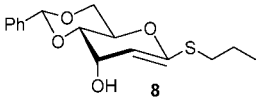
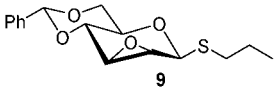
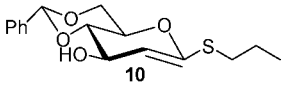
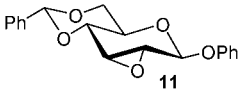
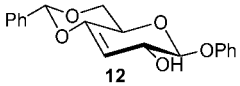
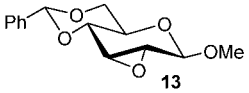
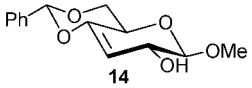
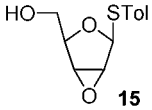
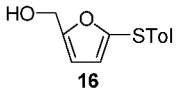
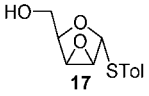
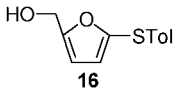
Table 1. Rearrangement of Carbohydrate Epoxides to Unsaturated Sugar Derivatives

entry	epoxide	allylic alcohol	solvent	base	condition	time	yield [%]
1	 **1**	 **2**	$PhCH_3$ – *n*-BuOH	NaOH	*n*-Bu_4NBr, reflux	1 h	99
2	 **3**	 **4**	$PhCH_3$ – *n*-BuOH	NaOH	*n*-Bu_4NBr, reflux	1.5 h	82
3	 **5**	 **6**	$PhCH_3$ – DMF – *n*-BuOH	NaOH	*n*-Bu_4NBr, reflux	0.5 h	89
4	 **7**	 **8**	DMF	*t*-BuOK	rt	2 h	80
5	 **9**	 **10**	DMF	*t*-BuOK	rt	2 h	100[a]
6	 **11**	 **12**	DMF	*t*-BuOK	*n*-Bu_4NBr, 90 °C	2 d	57
7	 **13**	 **14**	DMF	*t*-BuOK	80 °C	2.5 h	64
8	 **15**	 **16**	DMF	*t*-BuOK	70 °C	1 h	43
9	 **17**	 **16**	DMF	*t*-BuOK	70 °C	1 h	46

[a] Yield is based on NMR analysis.

experimental results, it appears that: (1) furanoside epoxides may further eliminate H_2O, after rearrangement, to form furan derivatives and (2) in the rearrangement of pyranoside epoxides, (*S*)-glycosides tend to form unsaturated sugars with the 1,2-double bond, while *O*-glycosides favor formation of products with the 3,4-double bond.

In conclusion, a simple and efficient method for rearranging 2,3-anhydro carbohydrates to unsaturated sugars has been developed. The chemistry disclosed in this paper expands the synthetic utility of sugar epoxides. The exceptionally mild reaction conditions and high stereoselectivity should make this an attractive method for the preparation of unsaturated carbohydrate derivatives. Due to the importance of unsaturated sugars, this rearrangement may find wide applications in carbohydrate-based drug discovery. The further investigation of some unsaturated sugars as potential glycosidase inhibitors is now in progress.

Acknowledgment. This work was financially supported by the National Natural Science Foundation of China, "973" grant from the Ministry of Science and Technology of China, and "985" program from the Ministry of Education of China.

Supporting Information Available: All experimental procedures and data for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL052128X