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# THE USE OF 2,6-ANHYDRO-2-THIO GLYCOPYRANOSYL FLUORIDE FOR A HIGHLY α-STEREOSELECTIVE GLYCOSYLATION

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Summary: The glycosylation of 2, 6-anhydro-1-fluoro-2-thioglycoside **1** with alcohols under various conditions proceeded smoothly at low temperature to give the corresponding α-glycosides in high yields, and the selectivity was highly independent on the conditions examined.

The selective creation of O-glycosidic linkage of 2,6-dideoxy sugar in glycosylation has been a long standing ploblem in organic chemistry and still one of the most challenging task for organic chemists.[1] In previous paper, we demonstrated a novel and efficient synthesis of 2,6-dideoxy-α-glycosides by use of phenyl 2,6-anhydro-1,2-dithio-D-altropyranosides as glycosyl donors to illustrate a highly stereocontrolled glycosylation.[2] Recently, glycopyranosyl fluoride[3] has been paid considerable attention as an efficient glycosyl donor as well as phenylthio glycoside. In this communication, we wish to report that 3,4-di-O-acetyl-2,6-anhydro-1-fluoro-2-thio-D-altropyranoside (**1**) was smoothly glycosylated with alcohols at low temperature by a variety of methods to give the corresponding α-glycosides which were easily converted into the 2,6-dideoxy-α-glycosides[2] in high yields.

The key glycosyl donor **1**[4] was readily prepared from **2**[2] (1.3 equiv NBS, 1.5 equiv DAST,[5] -25°C, 10min) in 84% yield. We first examined the glycosylation of the anomeric mixture of **1** by using cyclohexylmethanol (**3**) as the glycosyl acceptor with many kinds of reagents such as $SnCl_2$-$AgClO_4$[3a], $SnCl_2$-$ZnCl_2$, $SnCl_2$[3b], TMSOTf[3c], $Cp_2MCl_2$-$AgClO_4$ or $AgBF_4$ (M=Zr, Hf)[3d, 3e]. The results summarized as entries 1~6 in Table 1 showed that these reactions procceded at low temperature to give the α-glycoside with high stereocontrol in high to excellent yields even by the method which was not originaly developed for α-glycosides (entry 5). Remarkably, stereoselectivity of the glycosylations was highly independent on the conditions examined. Further **1** was found to glycosylate with even hindered alcohols **5** and **6** by using only $SnCl_2$ as an activator to afford the corresponding α-glycosides in high yields (entries 8 and 9).

These results indicated that 2,6-anhydro-1-fluoro-2-thio sugar should find wide application in the synthesis of 2,6-dideoxy-α-glycosides.

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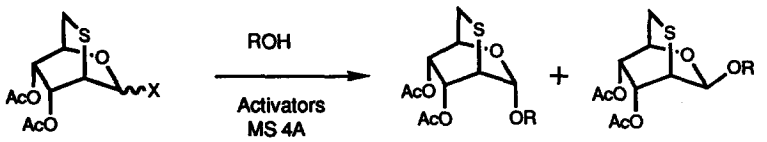
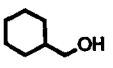
References and Notes:

1) See references and notes cited in ref. 2.
2) K. Toshima, S. Mukaiyama, T. Ishiyama, and K. Tatsuta, *Tetrahedron Lett.*, **31**, 3339 (1990).

**Table 1.** Glycosylations of 1 with alcohols by several conditions




**1:** X=F
**2:** X=SPh

| Entry | Alcohol[a] (R-OH) | Activators (equiv) | Solvent | Temp. | Time | Product[2] (α/β[c]) | Yield (%)[b] |
|---|---|---|---|---|---|---|---|
| 1 |  **3** | $SnCl_2$(1.1)-$AgClO_4$(1.1) | $Et_2O$ | -10°C | 90min | 97/3 | 98 |
| 2 | | $SnCl_2$(1.1)-$ZnCl_2$(1.1) | $Et_2O$ | -10°C | 90min | 98/2 | 89 |
| 3 | | $SnCl_2$(1.1) | $Et_2O$ | -10°C | 90min | 100/0 | 91 |
| 4[6] | | TMSOTf(1.0) | $Et_2O$ | -10°C | 90min | 92/8 | 90 |
| 5 | | $Cp_2HfCl_2$(5.0)-$AgClO_4$(5.0) | $CH_2Cl_2$ | -10→25°C | 90min | 93/7 | 95 |
| 6 | | $Cp_2ZnCl_2$(0.6)-$AgBF_4$(1.2) | $CH_2Cl_2$ | -20→10°C | 120min | 98/2 | 92 |
| 7 |  **4** | $SnCl_2$(1.1) | $Et_2O$ | -10°C | 90min | 98/2 | 94 |
| 8 |  **5** | $SnCl_2$(1.1) | $Et_2O$ | -10°C | 140min | 98/2 | 76 |
| 9 |  **6** | $SnCl_2$(1.1) | $Et_2O$ | -10°C | 90min | 96/4 | 81 |

a) All reactions were carried out by use of 2.0 equiv. of alcohol to the glycosyl donor.
b) Isolated yields after purification by column chromatography.
c) α:β Ratios were determined by $^1$H-NMR spectroscopy and /or isolation of pure isomers.


3) (a) T. Mukaiyama, Y. Murai, and S. Shoda, *Chem. Lett.*, **1981**, 431; (b) K. C. Nicolaou, T. Ladduwahetty, J. L. Randall, and A. Chucholowski, *J. Am. Chem. Soc.*, **108**, 2466 (1986); (c) S. Hashimoto, M. Hayashi, and R. Noyori, *Tetrahedron Lett.*, **25**, 1379 (1984); (d) T. Matsumoto, H. Maeta, K. Suzuki, and late G. Tsuchihashi, *Tetrahedron Lett.*, **29**, 3567, 3571, 3575 (1988); (e) K. Suzuki, H. Maeta, T. Suzuki, and T. Matsumoto, *Tetrahedron Lett.*, **30**, 6879 (1989).

4) $^1$H-NMR($CDCl_3$, 270MHz) spectra [δ(TMS), J(Hz)] are shown only for anomeric proton for **1**: 5.92 (23/25H, ddd, J=69.0, 2.1 and 1.6 Hz, H-1(α)), 5.94 (2/25H, dd, J=68.6 and 3.8Hz, H-1(β)).

5) K. C. Nicolaou, R. E. Dolle, D. P. Papahatjis, and J. L. Randall, *J. Am. Chem. Soc.*, **106**, 4189 (1984).

6) Only when $CH_3CN$ was used as a solvent in the glycosylation, β-anomer was predominantly obtained in high yield (88%, α/β=5/95).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