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Regioselective Protection of Sugars Catalyzed by Dimethyltin Dichloride

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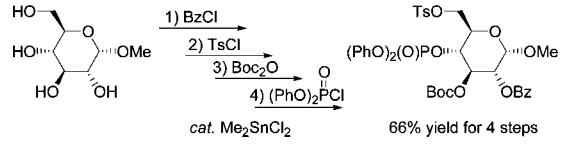
ABSTRACT



The first catalytic process for protection of hydroxyl groups in sugars has been developed. Highly regioselective protection was accomplished along with high chemical yield. The regioselectivity of the benzoylation was realized as an intrinsic character of sugars based on a stereorelationship among their hydroxyl groups. Furthermore, complete protection of α-methyl glucoside and β-methyl xyloside was accomplished.

Selective protection of hydroxyl groups in sugars is one of the most fundamental techniques in sugar chemistry since it is essential for selective functionalization of sugars including glycosidation.[1] For this purpose, some methods have been developed based on regioselective complexation of hydroxyl groups in sugars with tin or boron reagents.[2] These methods, however, require a stoichiometric amount of hazardous reagents. We have developed selective monobenzoylation of 1,2-diols using a catalytic amount of dimethyltin dichloride.[3] Also, the catalytic ability of dibutyltin reagent for activation of 1,2-diols has been demonstrated.[4] However, so far there is no literature applying organotin catalysts to regioselective protection of unprotected sugars.[5]

In this communication, we present the first catalytic process for protection of hydroxyl groups of sugars[6] in a highly regioselective manner using dimethyltin dichloride (Me_2SnCl_2) and its application to preparation of completely protected sugars.

We started off by treating sugars **1a**−**g** with 1.2 equiv of benzoyl chloride in the presence of DIPEA and 0.05 equiv of Me_2SnCl_2 in THF or aqueous THF to test their benzoylation. The results are summarized in Table 1.

In all cases, monobenzoylated sugars **2a**−**g** were regioselectively obtained in high to excellent yields. The monobenzoylation predominantly took place at the 1,2-diol moiety except for β-methyl glucoside (**2b**) where the primary hydroxyl group at the 6-position was selectively benzoylated (entry 2). For **1a**−**d**, anhydrous THF as a solvent was better than aqueous THF (entries 1−4), while aqueous THF (THF:H_2O = 9: 1) was more effective for

(1) Boons, G. J. *Tetrahedron* **1996**, *52*, 1095, and references cited therein.

(2) (a) Wagner, D.; Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem.* **1974**, *39*, 24. (b) Munavu, R. M.; Szmant, H. H. *J. Org. Chem.* **1976**, *41*, 1832. (c) Nashed, M. A.; Anderson, L. *Tetrahedron Lett.* **1976**, *17*, 3503. (d) Tsuda, Y.; Haque, M. E.; Yoshimoto, K. *Chem. Pharm. Bull.* **1983**, *31*, 1612. (e) Nicolaou, K. C.; van Delft, F. L.; Conley, S. R.; Mitchell, H. J.; Jin, Z.; Rodríguez, R. M. *J. Am. Chem. Soc.* **1997**, *119*, 9057. (f) Tsuda, Y. *J. Synth. Org. Chem. Jpn.* **1997**, *55*, 907. (g) Oshima, K.; Aoyama, Y. *J. Am. Chem. Soc.* **1999**, *121*, 2315.

(3) (a) Maki, T.; Iwasaki, F.; Matsumura, Y. *Tetrahedron Lett.* **1998**, *39*, 5601. (b) Iwasaki, F.; Maki, T.; Onomura, O.; Nakashima, W.; Matsumura, Y. *J. Org. Chem.* **2000**, *65*, 996.

(4) (a) Caddick, S.; McCarroll, A. J.; Sandham, D. A. *Tetrahedron* **2001**, *57*, 6305. (b) Burke, S. D.; Voight, E. A. *Org. Lett.* **2001**, *3*, 237. (c) Martinelli, M. J.; Vaidyanathan, R.; Pawlak, J. M.; Nayyar, N. K.; Dhokte, U. P.; Doecke, C. W.; Zollars, L. M. H.; Moher, E. D.; Khau, V. V.; Košmrlj, B. *J. Am. Chem. Soc.* **2002**, *124*, 3578.

(5) A preliminary result of this work was disclosed by us: Matsumura, Y.; Maki, T.; Iwasaki, F. *Jpn. Kokai tokkyo Koho 2001*; JP 2001247592: CA 135:242453, 2001.

(6) More recently, two excellent methods were reported. See: from per-*O*-silylated sugars by TMSOTf: (a) Wang, C.-C.; Lee, J.-C.; Luo, S.-Y.; Kulkarni, S. S.; Huang, Y.-W.; Lee, C.-C.; Cheng, K.-L.; Hung, S.-C. *Nature* **2007**, *446*, 896. By organocatalyst: (b) Kawabata, T.; Muramatsu, W.; Nishio, T.; Shibata, T.; Schedel, H. *J. Am. Chem. Soc.* **2007**, *129*, 12890.

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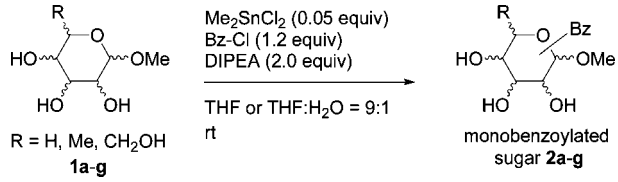
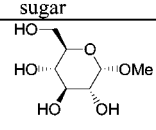
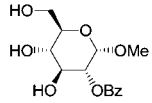
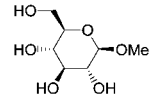
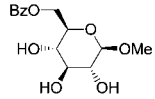
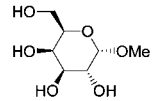
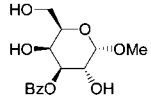
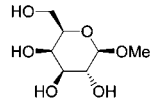
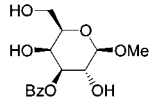
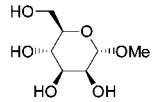
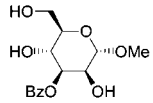
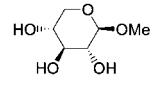
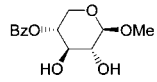
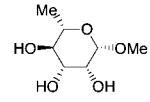
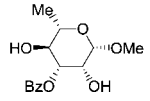
Table 1. Regioselective Monobenzoylation of Various Sugars[a]



entry	sugar		benzoylated sugar		yield (%)[b]
1		**1a**		**2a**	82[c] (61)[d]
2		**1b**		**2b**	79[c] (75)[d]
3		**1c**		**2c**	84[c] (50)[d]
4		**1d**		**2d**	91[c] (44)[d]
5		**1e**		**2e**	82[c] (97)[d]
6		**1f**		**2f**	72[c] (96)[d]
7		**1g**		**2g**	91[c] (96)[d]

[a] See Supporting Information for experimental details. [b] A small amount of dibenzoylated sugars was observed. [c] In THF. [d] In THF:H_2O = 9:1.

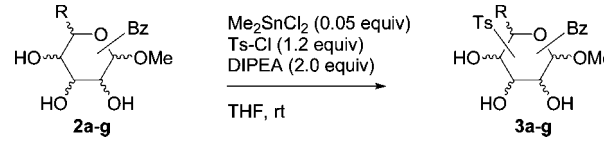
1e−**g** which are hardly soluble in anhydrous THF (entries 5−7). Although the benzoylation of α-methyl mannoside (**1e**) by dibutyltin or dioctyltin dichloride exhibited similar regioselectivity, the yields were low especially in reactions carried out in aqueous THF. The decrease in yields may be due to the bulkiness of the alkyl group.[7]

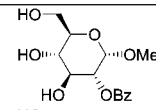
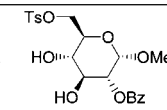
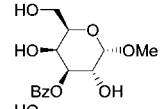
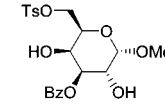
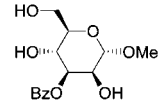
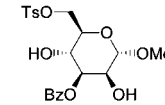
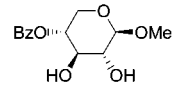
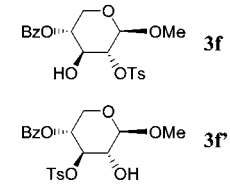
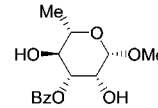
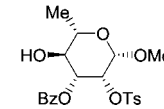
Monobenzoylated sugars **2a**,**c**,**e**,**g** were further monotosylated to give the corresponding **3a**,**c**,**e**,**g**without any acyl migration in consecutive treatment (Table 2, entries 1−3 and 5).[8] However, tosylation of O^4-benzoylated *β*-methyl xyloside (**2f**) proceeded in a low regioselective manner to afford a mixture of O^2- and O^3-tosylated products (**3f** and **3f′**) (entry 4). Moreover, tosylation of O^6-benzoylated *β*-methyl glucoside (**2b**) and O^4-benzoylated *β*-methyl galactoside (**2d**) gave complex mixtures.

(7) Compound **2e** was obtained in 48% for *n*-Bu_2SnCl_2 and 39% for $(n\text{-}C_8H_{16})_2SnCl_2$.

(8) By one-pot reaction without isolating the intermediates, **3a** and **4** were obtained starting from **1a** in 63% and 32% yield, respectively.

Table 2. Regioselective Tosylation of Monobenzoylated Sugars[a]



entry	sugar		tosylated sugar		yield (%)
1		**2a**		**3a**	88
2		**2c**		**3c**	65
3[b]		**2e**		**3e**	85
4		**2f**		**3f** **3f′**	64[c]
5		**2g**		**3g**	50

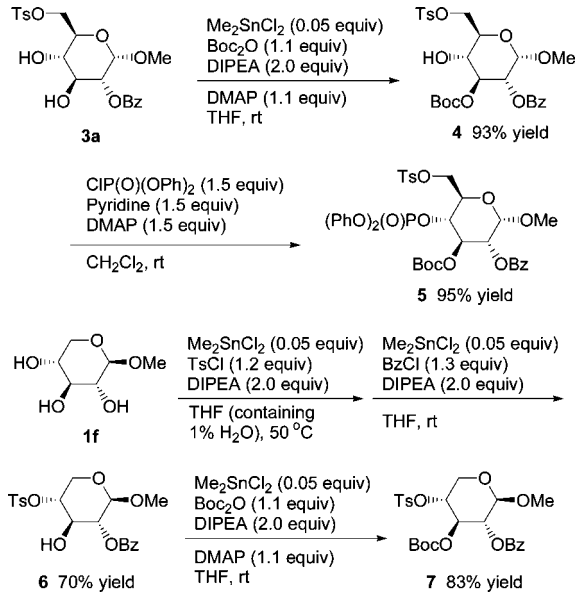
[a] See Supporting Information for experimental details. [b] 0.1 equiv of DMAP was added. [c] A mixture of O^2- and O^3-monotosylated (**3f**: 26% and **3f′**: 38%) was obtained.

α-Methyl glucoside derivative **3a** was *t*-butoxycarbonylated at the 3-position catalyzed by Me_2SnCl_2 to give **4** in 93% yield regioselectively, while phosphorylation of **4** afforded completely protected glucoside **5** in 95% yield (Scheme 1). Full protection of *β*-methyl xyloside (**1f**) was carried out as follows. Monotosylation of the 4-hydroxyl group in **1f** and successive monobenzoylation of the 2-hydroxyl group afforded **6**. Finally, *t*-butoxycarbonylation of **6** gave **7** in satisfactory yield.

Fully protected α-methyl glucoside **5** was treated with NaN_3 to give the 6-azido sugar **8**. The azide group in **8** could be reduced to give the 6-amino sugar **9** or subjected to cycloaddition with phenyl acetylene in the presence of catalytic $CuSO_4$ to give the 6-triazole sugar **10** (Scheme 2).

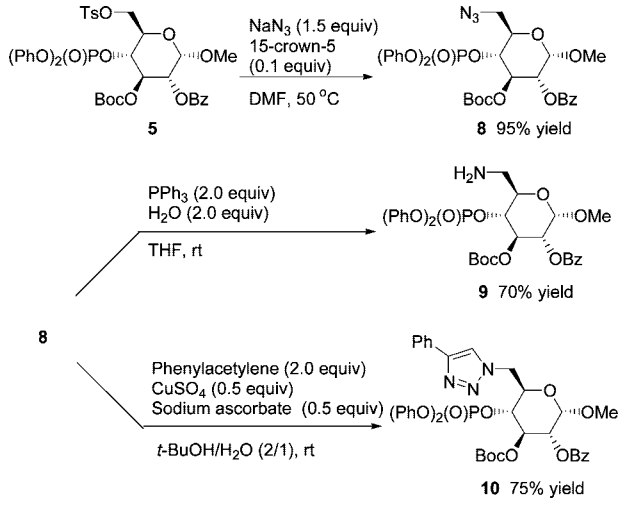
The regioselectivity of monobenzoylation of these sugars can be explained as follows: Me_2SnCl_2 can loosely interact with sugars and can move freely among diol moieties on sugars. Since the coordination of metal ions may increase the acidity of hydroxyl groups, they are readily deprotonated by even a weak base such as DIPEA. Thus, the most accessible hydroxyl group of 1,2-diol moieties may be attacked by DIPEA and benzoylated. The accessibility can be explained according to a simple rule (Figure 1). Obviously, an equatorial substituent adjacent to the reacting hydroxyl group is restricting the approach of DIPEA. From

Scheme 1. Successive Protection of α-Methyl Glucoside and *β*-Methyl Xyloside



this point of view, sugars **1a**,**d**,**e**,**f**,**g** in their preferred conformations have a single equatorial hydroxyl group which has an adjacent carbon atom with an equatorial hydrogen atom (Figure 1b), whereas in **1b**, no secondary alcohol has an adjacent carbon atom bearing an equatorial hydrogen

Scheme 2. Application for α-Methyl Glucoside Derivative **5**



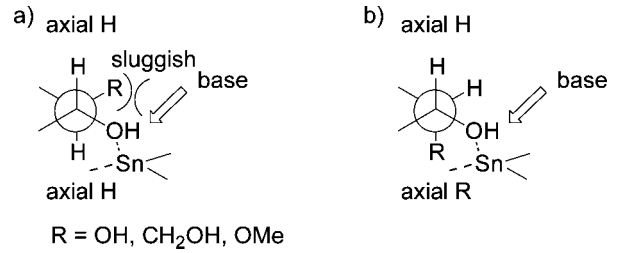


Figure 1. Plausible explanation for regioselective protection of sugars by tin catalyst.

atom. Therefore, the primary alcohol becomes more reactive than the secondary one which is in the situation depicted in Figure 1a. Although sugar **1c** has two equatorial OH groups at the 2- and 3-position, O^3-benzoylated sugar **2c** was exclusively obtained. It is still unclear why the 3-OH group of **1c** was more reactive than the 2-OH group. One of the reasons may be probability, that is, the 3-OH of **1c** has two possibilities (2,3- and 3,4-complexation) to form active complexes, and the 2-OH has only one (2,3-complexation).

In conclusion, we have developed the first catalytic process for protection of hydroxyl groups in sugars. Highly regioselective protection was accomplished along with high chemical yield. The regioselectivity of the benzoylation was realized as an intrinsic character of sugars based on a stereorelationship among their hydroxyl groups. Furthermore, complete protection of α-methyl glucoside and *β*-methyl xyloside was accomplished. The findings presented here will greatly contribute not only to the development of a direct manipulation method of unprotected sugars but also to a better understanding of sugar−metal ion interaction and its activation process.[9] Design of new sugar-recognizing catalysts and their application for catalytic functionalization of sugars are current subjects of our focus.

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Supporting Information Available: Experimental section and spectroscopic data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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