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Organotin-catalyzed regioselective benzylation of carbohydrate *trans*-diols

Hengfu Xu[a,c], Ying Zhang[b,c], Hai Dong[b,*], Yuchao Lu[a], Yuxin Pei[a], Zhichao Pei[a,*]

[a] *College of Chemistry and Pharmacy, Northwest A&F University, Yangling 712100, Shaanxi, PR China*
[b] *School of Chemistry & Chemical Engineering, Huazhong University of Science & Technology, Luoyu Road 1037, 430074 Wuhan, PR China*

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ABSTRACT

A convenient approach to regioselective benzylation of carbohydrate *trans*-diols was developed, where 0.1 equiv. of Bu_2SnCl_2 and 0.1 equiv. of TBABr were used as the catalysts and 2.0 equiv. of BnCl was used as the benzylation reagent. In most cases, similar or better benzylation regioselectivities and isolated yields were obtained by using catalytic amounts of Bu_2SnCl_2, rather than stoichiometric amounts of organotin reagents required.

Introduction

Regioselective protection strategy plays a very important role in carbohydrate chemistry due to the modification to specific hydroxyl groups of carbohydrates and the construction of suitable building blocks for the synthesis of oligosaccharides.[1–17] Organotin reagents have been widely used in regioselective protection strategies due to the relatively straightforward manipulation and high regioselectivity and reliability.[18,19] The methods have a broad substrate scope, including 1,2-diols, 1,3-diols, *cis*-diols, *trans*-diols and polyols. Though the regioselectivities for *trans*-diols are moderate in many cases, the methods are certainly useful to avoid the wasteful formation of di-benzylation side products. A cyclic dioxolane-type intermediate formed by organotin with two adjacent hydroxyl groups plays a key role for selectivities in the reaction, due to stereo and stereoelectronic effects of the dioxolane intermediate.[20–22] However, stoichiometric amounts of organotin reagents had to be used in these methods (Fig. 1a), which are not environmental-friendly due to the inherent potential toxicity of organotin reagents.[23,24] Therefore, several methods in which nontoxic alternatives to organotin or reduced amount of organotin species are used have been developed.[25–38] However, these methods usually only lead to good regioselectivities for substrates containing 1,2-diols, 1,3-diols, and *cis*-diols. Thus, there is an urgent requirement to develop a selective protection method for substrates containing *trans*-diol in which the use of stoichiometric amounts of organotin can be avoided. In the present study, an efficient method for selective benzylation of carbohydrate *trans*-diols was developed (Fig. 1b), where 0.1 equiv. of Bu_2SnCl_2 was used instead of stoichiometric amounts of organotin. In most cases, similar or better benzylation regioselectivities were obtained compared to using stoichiometric amounts of organotins.

Results and discussion

We have previously developed an organotin-catalyzed regioselective benzylation method for *cis*-diols where 0.1 equiv. of dibutyltin oxide was used as the catalyst and 2.0 equiv. of BnBr was used as the benzylation reagent.[32] In this study, in order to explore why that method led to poor selectivities for the benzylation of carbohydrate *trans*-diols, *trans*-diol methyl 4,6-*O*-benzylidene-α-D-glucopyranoside **1** was chosen to be benzylated through the use of various amounts of dibutyltin oxide. The experimental results showed that the ratio of 2-OBn product **2a** and 3-OBn product **2b** increased from 1:0.9 to 1:0.3 by increasing the amount of dibutyltin oxide from 0.1 equivalents to 1.1 equivalents.

In comparison with direct benzylation of *trans*-diol **1** leading to no selectivity (Fig. 2a), when stoichiometric amounts of organotin are used, all *trans*-diol **1** firstly turns to cyclic dioxolane-type

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* Corresponding authors.
E-mail addresses: hdong@mail.hust.edu.cn (H. Dong), peizc@nwafu.edu.cn (Z. Pei).
[c] These authors contributed equally to this work.

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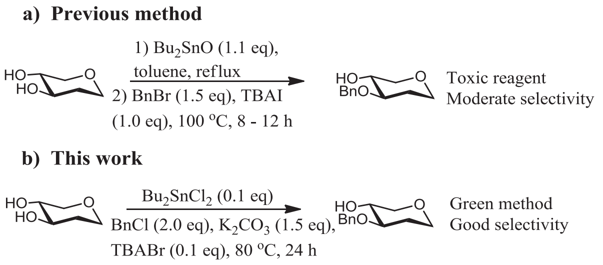


Fig. 1. Comparison of the present method with previous reported methods.

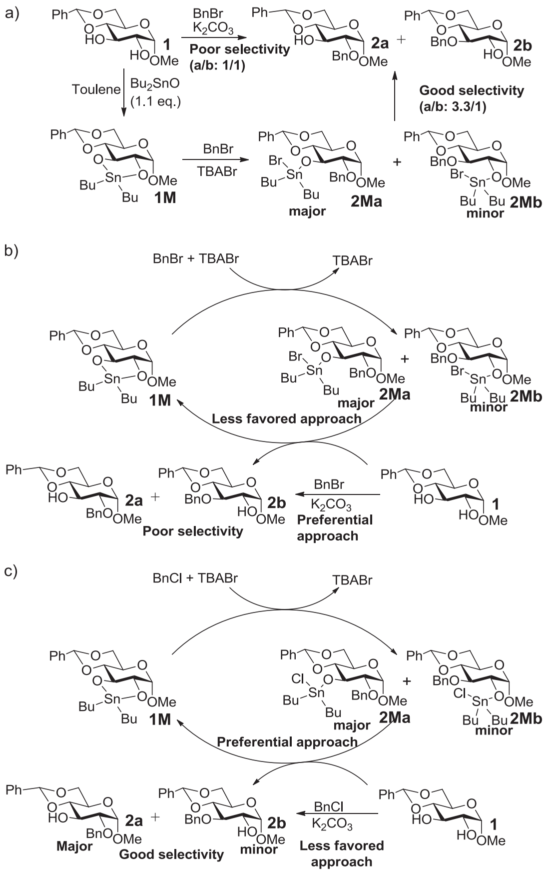
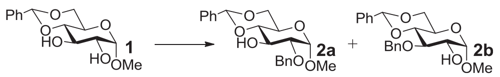


Fig. 2. Proposed benzylation process: a) comparison of direct benzylation with the benzylation using organotin reagents; b) inefficient catalytic process by organotin with BnBr as the benzylation reagent due to the preferential direct benzylation over the regeneration of the dibutylstannylene acetal intermediate; c) efficient catalytic process by organotin with BnCl as the benzylation reagent.

Table 1

Comparison of results by variation from "standard" conditions.



Entry	Conditions	NMR Ratio (**2a**:**2b**)
1	Standard conditions[a]	2:1 (65:30)[b]
2	No Bu_2SnCl_2	1:1
3	No TBABr	1:1
4	No K_2CO_3	No reaction
5	Me_2SnCl_2 instead of Bu_2SnCl_2	1.6:1
6	Ph_2SnCl_2 instead of Bu_2SnCl_2	1.8:1
7	BnBr instead of BnCl	1.2:1
8	PMBCl instead of BnCl	1.4:1
9	DMF instead of MeCN	Low reactivity
10	PhMe instead of MeCN	1:1

Reaction conditions: [a]substrate **1** (70 mg), Bu_2SnCl_2 (0.1 equiv.), TBABr (0.1 equiv.), K_2CO_3 (1.5 equiv.), BnCl (2 equiv.), acetonitrile (2 mL), 80 °C, 24 h. [b]Isolated yield.

intermediates **1M** which further react with BnBr to form major **2Ma** and minor **2Mb**, thus leading to good selectivity. Based on this, if a catalytic amounts of organotin were used, the regeneration of the cyclic dioxolane-type intermediate **1M** would be vital to the efficient catalytic process. Therefore, the inefficient catalytic process[32] for benzylation of *trans*-diol **1** must be due to the preferential direct benzylation over the regeneration of **1M** via the transformation of organotin species from intermediates **2Ma** and **2Mb** to *trans*-diol **1** (Fig. 2b). In other words, the efficient catalytic process for benzylation of *trans*-diol **1** would proceed if the regeneration of **1M** were preferential over the direct benzylation. This inspired us to use BnCl as the benzylation reagent instead of BnBr in the catalytic process (Fig. 2c). Since the reactivity of BnCl is much less than that of BnBr in the substitution reaction, we hypothesized that the direct benzylation of *trans*-diol **1** with BnCl would be less favored than the regeneration of the intermediate **1M**, leading to good selectivity of 2-OBn product **2a**.

The hypothesis was further supported by the selective benzylation of *trans*-diol **1** where 0.1 equiv. of Bu_2SnCl_2 and 0.1 equiv. of TBABr were used as the catalysts and 2.0 equiv. of BnCl was used as the benzylation reagent (Table 1). Under the standard conditions, *trans*-diol **1** (70 mg) was allowed to react with 2.0 equiv. of BnCl in the presence of 0.1 equiv. of Bu_2SnCl_2, 0.1 equiv. of TBABr and 1.5 equiv. of K_2CO_3 in acetonitrile at 80 °C for 24 h. The NMR ratio of products **2a** and **2b** appeared 2:1 and the ratio of the corresponding isolated yields was 65:30 (Entry 1 in Table 1). Without Bu_2SnCl_2 or TBABr, the NMR ratio dramatically decreased to 1:1 (Entries 2 and 3 in Table 1), whereas, without K_2CO_3 no reaction occurred (entry 4 in Table 1). With Me_2SnCl_2 or Ph_2SnCl_2 instead of Bu_2SnCl_2, the NMR ratio of **2a** and **2b** decreased to 1.6:1 and 1.8:1 respectively (Entries 5 and 6 in Table 1), which might reflect the steric effect of alkyl groups in organotins. Using BnBr or PMBCl instead of BnCl, the NMR ratio decreased to 1.2:1 and 1.4:1 respectively (Entries 7 and 8 in Table 1), which reflect the reactivities of the benzylation reagents. The more direct benzylation of **1** by benzylation reagents with higher reactivity led to poorer regioselectivity (Fig. 2b). DMF as the solvent led to low reactivity (Entry 9, Table 1), and toluene as the solvent led to no selectivity (Entry 10, Table 1).

The method was further tested with methyl 4,6-*O*-benzylidene glycoside *trans*-diols **3**, **5** and **7** (Entries 1–3 in Table 2). The ratio of benzylation products **4a**/**4b**, **6a**/**6b** and **8a**/**8b** were 66/19, 30/70 (NMR ratio) and 21/70 respectively. In comparison with these results, the ratio of **4a**/**4b**, **6a**/**6b** and **8a**/**8b** were 48/32, 43/57 (NMR ratio) and 38/46 respectively when BnBr was used instead of BnCl as the benzylation reagent in the method. It has been summarized that only *trans*-diols where one adjacent substituent is equatorial and one is axial exhibit good selectivities on the hydroxyl groups adjacent to the axial substituent in the benzylation using stoichiometric amounts of organotins.[18] For example, *trans*-diols **1** and **7** usually exhibited good selectivities[39] and *trans*-diols **3** and **5** usually exhibited poor selectivities[40,41] when using stoichiometric amounts of organotin reagents. The resulted regioselectivities has been proposed to be caused by stereo and stereoelectronic effects.[21] Interestingly, all these four diols (**1**, **3**, **5** and **7**) exhibited good selectivities in the organotin-catalyzed method. Furthermore, azido 4,6-*O*-benzylidene glycoside *trans*-diols **9** and **11** exhibited higher selectivities with this method. It can be seen that products **10**, where the 2-position is selective benzylated, and **12**, where the 3-position is selective benzylated, were isolated