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A More Convenient and General Procedure for *O*-Monobenzylation of Diols via Stannylenes: A Critical Reevaluation of the Bu_2SnO Method

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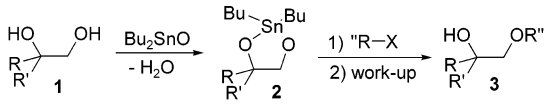
Abstract: A more consistent, straightforward, and economical protocol for generation of stannylene species and their reaction with BnBr leading to products of *O*-monobenzylation of diols has been set. It has shown to be specially indicated for substrates bearing vicinal trans 1,2-diol moieties on cyclohexane backbones, which are more resistant to these transformations. Such protocol has been successfully applied to *myo*-inositol derivatives and acyclic diols.

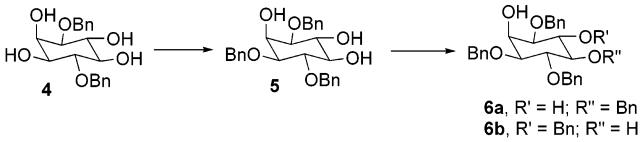
The introduction of tributyltin ethers and dibutylstannylene acetals derived from alcohol and diol moieties, respectively, provided a major leap to carbohydrate chemistry, most notably.[1] On reacting with activated alkyl halides (the main use of these organometallic intermediates), they combine an adequate nucleophilicity with a negligible basicity. Stannylene acetals **2** (Scheme 1) are produced by reaction of diol moieties **1** and Bu_2SnO.[1,2] Such species may undergo substitution to **3** under essentially neutral conditions. Remarkable features of these reactions are the regiochemical (substitution on primary hydroxyl groups prevails over those on secondary or tertiary ones) and stereochemical (equatorial hydroxyl groups, and not axial ones, react preferentially) controls that they enable. Besides, the Bu_2SnO method is able to selectively afford *O*-monosubstituted diol moieties even in the presence of other unprotected hydroxyl groups. Due to such assets, this powerful methodology is not paralleled by anionic chemistry, which usually leads to mixtures of isomers.[1]

In the course of our studies on inositol chemistry, we were required to prepare large amounts of tetrabenzyl ethers **6a** and **6b** (Scheme 2). After some disappointing results of direct dibenzylation of tetrol **4** via (bis)stannylene acetals,[3] we realized that the stepwise process (through triol **5**) would yield a more consistent route to those materials. However, the early work with these two reactions indicated that there was some space for procedure improvement. The development of a protocol for general application was clearly demanded.

SCHEME 1. Selective *O*-Monobenzylation of Diols via Stannylene Acetals



SCHEME 2. Synthesis of *myo*-Inositols 5 and 6



On inspection of representative examples within the vast collection of data in the literature dealing with the use of stannylene acetals, we noticed an uncertainty on the conditions actually needed for both the tin intermediate generation and, more importantly, its reaction with alkylating agents such as BnBr. As the following discussion demonstrates, such indecision does not seem to be reasonable whatsoever. Apparently, it is not related to the molecular diversity of the suitable substrates.

First, we concluded that the stannylene intermediate formation does not require H_2O removal (e.g., by use of Dean−Stark apparatus), as it is observed in most of the works in the literature.[4,5] A simple reflux of the reactants in CH_3OH/toluene, followed by careful evaporation of the solvents suffices for the reactions of both cyclic substrates (bearing either *cis*-diol or trans-diol moieties) and acyclic ones, as the following results will confirm. This aspect is particularly important if it is taken into account that the unnecessary use of the Dean−Stark apparatus requires bath temperatures well above the reflux ones (140−150 °C in the case of toluene as solvent). So, when subjected to the mentioned conditions, *myo*-inositols **4** and **5** were converted to stannylene acetals **7** and **8** (Figure 1), respectively.

For the benzylation of the tin species **7**, we chose the Veyrières−David conditions.[6] Reaction of this organometallic compound with BnBr in toluene in the presence of Bu_4NBr (0.2 molar equiv; condition A of stannylene alkylation) occurred uneventfully to provide **5** (Table 1, entry 1). It is not necessary to employ either stoichiometric or excess amounts of ammonium halide additive,[7]

(1) David, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 643.
(2) Augé, C.; David, S.; Veyrières, A. *J. Chem. Soc., Chem Commun.* **1976**, 375.
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(5) The exceptions almost invariably deal with the preparation of stannylenes from cis diol moieties on furanoside backbones, following the pioneering work of Moffatt's group: Wagner, D.; Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem.* **1974**, *39*, 24. Boger, D. L.; Ichikawa, S.; Zhong, W. *J. Am. Chem Soc.* **2001**, *123*, 4161. Danishefsky, S. J.; Hungate, R.; Schulte, G. *J. Am. Chem. Soc.* **1988**, *110*, 7434.
(6) (a) David, S.; Thieffry, A.; Veyrières, A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1796. (b) Veyrières, A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1629.

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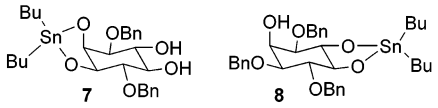

FIGURE 1. Monomeric structures of stannylene acetals **7** and **8**.

TABLE 1. *O*-Monobenzylation of Diol Moieties via the Optimized Bu_2SnO Method

entry	substrate	product (s)	yield (%)	conditions[a]	reaction time (h)
1	**4**	**5**	77	A	4
2	**5**	**6a, 6b** (1:1.4)[b]	70	B	9.5
3	**9**	**6a**	89	A	2.5
4	**10**	**11a, 11b** (1:1.5)[b]	72	B[c]	6
5	**12**	**10**	93	B[d]	6
6	**13**	**14**	93	A	1.5
7	**15**	**16**	78	A	1.5

[a] Condition for stannylene acetal reaction with BnBr: (A) BnBr (2.0 molar equiv); Bu_4NBr (0.2 molar equiv), toluene, 130 °C; (B) same as A, except for Bu_4NBr (0.6 molar equiv). [b] Respectively. [c] 3.5 molar equiv of BnBr was employed. [d] 2.5 molar equiv of Bu_2SnO and 3.0 equiv of BnBr were employed.

a common feature of these reactions in the literature, to achieve high rates and chemical yields. Moreover, Bu_4NBr successfully replaces more expensive Bu_4NI.[6a] Extension of the same benzylation condition to the reaction of stannylene **8** did not reproduce the satisfactory results obtained for **7**. Species **8** (whose stannylene portion was built on a *trans*-diol moiety) is clearly more resistant to alkylation. Besides slow reaction, conversion to **6a** and **6b** was not complete after >15 h (41% based upon 29% of recovered starting material; **6b**/**6a** ratio = 1.2:1.0, respectively). Adding 0.2 molar equiv of Bu_4NI to the previous reaction mixture in order to generate more reactive BnI in situ actually managed to accelerate the transformation. Substrate consumption was essentially complete (6.5 h), and product ratio also changed (**6b**/**6a** ratio = 2.5:1.0, respectively). However, higher conversion was not followed by the corresponding yield increase (43% yield), which may indicate product/substrate degradation. Thus, at least in (more desirable) lesser quantities and with resisting substrates, the employment of Bu_4NI (an indication of the original procedure)[6a] does not seem to afford the best results.

As a matter of fact, we found that a modest increase in Bu_4NBr quantity led to a very satisfactory reaction. Stannylene **8** reacted with BnBr (2.0 molar equiv) in the presence of a still substoichiometric amount of Bu_4NBr (0.6 molar equiv; condition B of stannylene alkylation) providing tetrabenzyl ethers **6a** and **6b** (Table, entry 2) in an efficient manner. It is noteworthy that, even in more difficult benzylations, it is possible to achieve a satisfactory compromise between efficiency (yields and rates) and reaction economy.

This straightforward protocol involving easy generation of stannylene acetals and differential conditions A/B for benzylation was successfully applied to various substrates (Figure 2). Triol **9** underwent fast monobenzylation at C_3-hydroxyl to **6a** through benzylation condition

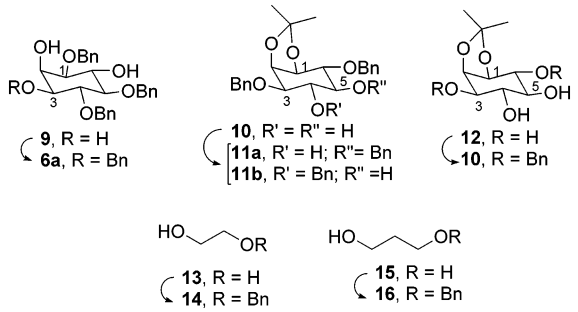

FIGURE 2. Additional substrates and products of *O*-monobenzylation of diol moieties.

A, as had occurred with compound **4** (Table, entry 3). On the other hand, acetal **10**, bearing a trans vicinal diol moiety, as expected, was more resistant to alkylation. Employment of condition B nonetheless led to tribenzyl ethers **11a** and **11b** in good yields and a satisfactory reaction time (Table, entry 4). In cases such as those of substances **5** and **10**, it is rewarding to employ a slightly higher amount of BnBr (3.5 molar equiv).

Gigg et al. showed that the bis-stannylene generated from acetal **12** can be regioselectively dibenzylated at C-3 and C-6 hydroxyl groups to **10**.[8] We applied our general protocol (condition B) to this interesting transformation and, thus, achieved a better reaction profile (Table, entry 5). Besides a markedly higher yield (93% against literature 63%),[8a] the reaction proceeded considerably faster with the same 0.6 molar equiv of the ammonium salt additive. Dibenzyl ether **10** and other dialkylated counterparts have been shown to be preeminent starting materials in the synthesis of bioactive inositol derivatives.[9]

We also studied the replacement of toluene for CH_3CN as the solvent for the stannylene benzylation step as prescribed by a few works in the literature.[10] The former one proved superior. For instance, in the monobenzylation of triol **9** in CH_3CN at 90 °C, 27% of starting material was recovered after 6−7 h, while in toluene at the same temperature, this reaction was carried out in less than 5 h. Furthermore, the dibenzylation step in the reaction of acetal **12** (whose reaction we have already demonstrated to afford an excellent result via our protocol) in CH_3CN at 90 °C did not occur completely after 15−17 h affording both the desired diether **10** (only 33%) along with a more polar fraction composed by an inseparable mixture of ethers benzylated at C-3 and C-6-hydroxyl groups. Of course, this result is partially justified by the lower reaction temperature imposed by the use of CH_3CN. That regioisomeric mixture was monobenzylated to produce **10** through the Bu_2SnO method. The low rates observed with this solvent may also be related to the issue of stannylene solubility, as the reaction mixtures in CH_3CN were heterogeneous.

Finally, we wondered whether our procedure could be extended to acyclic diols. Good results of *O*-benzylation

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(8) (a) Desai, T.; Gigg, J.; Gigg, R.; Martín-Zamora, E.; Schnetz, N. *Carbohydr. Res.* **1994**, *258*, 135. (b) Gigg, J.; Gigg, R.; Martín-Zamora, E. *Tetrahedron Lett.* **1993**, *34*, 2827.

(9) Ballereau, S.; Guédat, P.; Poirier, S. N.; Guillemette, G.; Spiess, B.; Schlewer, G. *J. Med. Chem.* **1999**, *42*, 4824. See also refs 7a and 8b.

(10) See refs 7a,b and 8.

of **13** (to **14**) and **15** (to **16**) show that this is indeed the case (Table 1, entries 6 and 7).

The application of this protocol to the alkylation with other compatible electrophiles (allyl and crotyl bromides, *p*-methoxybenzyl bromide) will further expand its scope. The more consistent reaction conditions advanced herein may facilitate initial experiments (small scales) involving stannylene acetals. It will also be useful in large-scale preparations enabling easier product purifications. And last but not least, this procedure may provide a safer ground for reaction optimization in the prospective cases of even more recalcitrant substrates (than diols **5** and **10**).

Experimental Section

General Methods. Toluene was distilled from benzophenone/Na^0. BnBr was treated with CaH_2, decanted, transferred to a dry distillation apparatus, and purified under vacuum. Crude products were purified by medium-pressure column chromatography and eluted (AcOEt/hexanes or AcOEt/toluene mixtures) on 230−400 mesh silica gel.

General Procedure. A mixture of the diol (1.0 mmol) and Bu_2SnO (1.0−1.2 mmol) in CH_3OH/toluene (1:1) (2−4 mL) was heated to 130 °C for 3 h. The solvents were evaporated, dry toluene (4 mL) was added to the residue, and a second evaporation to dryness was effected, which was completed under high vacuum. Then, a mixture of the crude stannylene derivative, Bu_4NBr (0.2 mol), and BnBr (2.0 mmol) (condition A of stannylene alkylation) in dry toluene (2−4 mL) under argon was heated to 130 °C until the reaction went to completion. After solvent evaporation, the residue was purified by chromatography. This procedure is essentially maintained for both condition B and *O*-dibenzylation of inositol acetal **12** (see text and Table 1 for details).

Substances **5**,[7a] **6**(**a**,**b**),[3] **10**,[8a] and **11**(**a**,**b**)[7b] (all racemic) are known substances. Their physical data were consistent with those of literature. Commercial samples of substances **14** and **16** are available.

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