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Competition of Deprotonation and Tin-Lithium Exchange in the Generation of a Glycosyl Dianion

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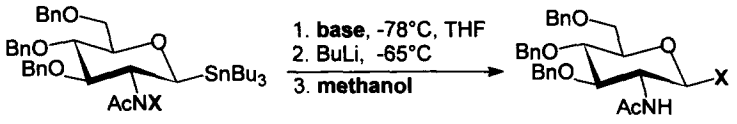
Abstract: The deprotonation and the tin-lithium exchange of the glycosylstannane **1** are not decoupled when BuLi is used. Deuteration experiments show that the side product **2H** (glycitol) is formed during the deprotonation/transmetallation reaction sequence and not by subsequent protonation of the glycosyl dianion. Decoupling of the two reaction steps is possible by using MeLi*LiBr for deprotonation and BuLi for tin-lithium exchange. The described procedure optimizes the preparation of a β-lithium-configurated glycosyl dianion by preventing the reduction side reaction. © 1997 Elsevier Science Ltd. All rights reserved.

Recently we reported a stereoselective synthesis of either α- or β-*C*-glycosides from glucosamine via glycosyl dianions.[1,2] The α-configurated glycosyl dianion was generated via deprotonation/reductive lithiation, the β-configurated via deprotonation/transmetallation.[3] Subsequent addition of electrophiles gave *C*-glycosides in up to 80% yield. The only significant side product for both reactions was the corresponding glycitol **2H**. It was assumed that the high basicity of the intermediate glycosyl dianions is responsible for the side product by taking up a proton from the protecting groups (benzyl ether) or the solvent (THF). Now we have performed several deuteration experiments to elucidate the source of protonation (**Scheme 1**) and to optimize the generation of a β-configurated glycosyl dianion.



1X X = H, D **2X**

Scheme 1

The results of the experiments are summarized in the Table. All reactions provided the glycitols **2H,D** in quantitative yield. The ratio of the two different glycitols **2** are simply determined from ^{1}H NMR spectra (Figure) since the ^{2}H NMR spectrum (from experiment **a**) confirmed that no α-deuterated product was formed (spectrum not shown). This spectrum also revealed that no deuterium was incorporated into the benzyl ether protecting groups.

The source of protonation was found when the glycosylstannane **1D** deuterated at the amide nitrogen was used for the generation of the glycosyl dianion (experiment **b**). Treating this reaction by *non-deuterated* methanol yielded a mixture of glycitols **2** where **2D** was present in an amount of 16%, i. e. about the same amount (18%) as the protonation product **2H** in experiment **a**. Hence, the amide hydrogen is the main protonation source. It is evident that the side product is already formed during the generation of the glycosyl dianion when the amide group is not yet deprotonated completely. This result was unexpected because the tin-lithium exchange for **1H** is slow at -78°C: The dianion formation can be followed by the progress of the red colouring and takes about 15 min to complete at this temperature while at -65°C the colouring occurs immediately. Deprotonation and metal exchange were separated by applying first MeLi*LiBr (experiment **c**) followed by addition of BuLi for tin-lithium exchange (1.3 eq. BuLi, -65°C, 2 min). Even an excess of MeLi*LiBr gave no transmetallation of the stannane **1H**.[4] Less successfully but interesting to differentiate between an inter- or intramolecular protonation reaction pathway is the use of LDA for deprotonation (experiment **d**). This base deprotonates the amide and forms itself the weak acid diisopropylamine. Therefore, 2.3 eq. of BuLi were used for the second reaction step, 1 eq. BuLi was added to reform LDA.

Table: Results of deuteration experiments for **1X** by using different bases.

experiment	**1**	base (1.0 eq.)	methanol	ratio (%)
a	**1H**	BuLi	D_3-MeO**D**	**2D** = 82 **2H** = 18
b	**1D**	BuLi	MeO**H**	**2D** = 16 **2H** = 84
c	**1H**	MeLi*LiBr	D_3-MeO**D**	**2D** = 98.4 **2H** = 1.6
d	**1H**	LDA	D_3-MeO**D**	**2D** = 89 **2H** = 11

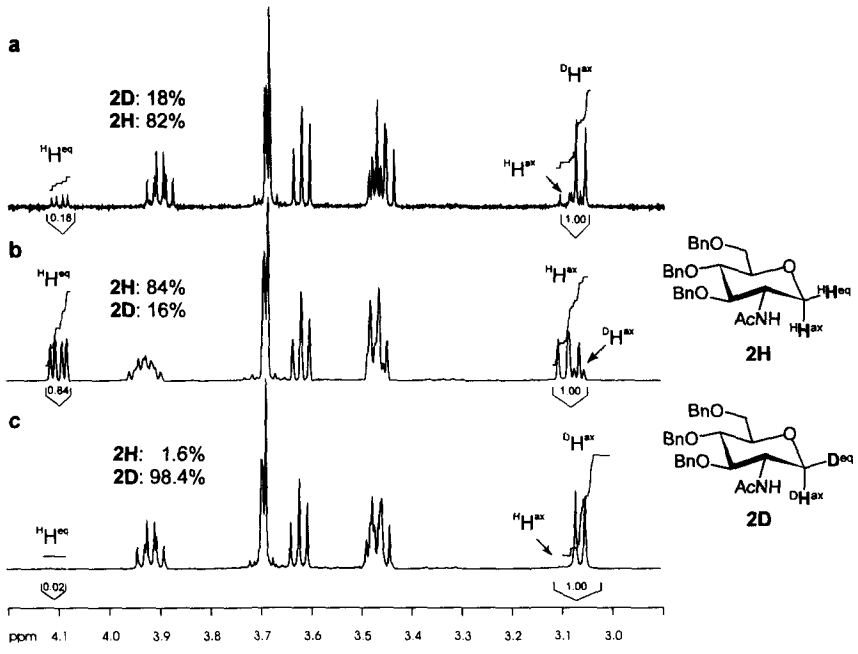
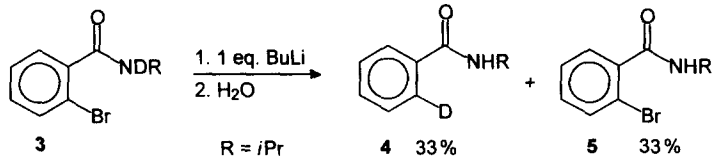


Figure: ^{1}H NMR (500 MHz, $CDCl_3$, 300K) spectra of the glycitols **2** from experiment **a**, **b** and **c**.

The literature gives little information about the scope of this protonation side reaction resulting from the conversion of tin compounds bearing proton donating groups and alkyllithiums.[5] In most cases the protonation product is probably less than 20%.[5] However, one communication documented a preferred reaction of BuLi at the tin center in the presence of an acidic carbamate. This stannane gave with one equivalent of BuLi the destannylated compound in 93% yield.[6] In comparison, the reaction of aromatic compounds which bear both acidic protons and halogen with alkyllithiums was already subject for intense investigations.[7-8] For example, the treatment of *N*-deuterio-*N*-isopropyl-*o*-bromobenzamide **3** with one equivalent of butyllithium followed by addition of water provided equal amounts of **4** and **5** (Scheme 2).[8] Mechanistic studies of these reactions indicate that either the halogen-lithium exchange is faster than the deprotonation[7] or the partially formed dianion reacts already with the starting material to provide the protonated compound.[8-9]



3 **4** 33% **5** 33%

Scheme 2

It is plausible that the side product in our experiment is formed in a similar way. We believe that a dianion reaction pathway is more likely than a competing deprotonation/tin-lithium exchange since under low mixing conditions red streaks which start from the added BuLi were observed. We assume that a glycosyl dianion intermediate (red colour) is formed during the mixing process of a drop of warm and highly concentrated BuLi (1.6 M in hexanes) and the cold stannane solution.

Having uncovered the origin of the formation of protonated glycitol side product, it was possible to optimize the procedure of a glycosyl dianion. Based on this observation the modified synthetic protocol increased also the yield of desired *C*-glycosides.

Acknowledgement.

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4 Alternatively, the halogen free MeLi (THF/Cumol 1:9, Cl < 0.07) may be used for deprotonation although we observed partial tin-lithium exchange under following conditions (**2H**: 2%, **2D**: 39%): 1) 1 eq. MeLi, -78°C. 2) 1.3 eq. MeLi, -65°C, 20 min.

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