Sodium hydride/hexamethylphosphoric triamide: a new and efficient reagent towards the synthesis of protected 1,2- and 5,6-enopyranosides

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A new method for the elimination of hydrogen halides and *p*-toluenesulfonic acid from sugar moieties using sodium hydride (NaH) in hexamethylphosphoric triamide (HMPA) at room temperature is reported. NaH/HMPA has several advantages compared to NaH/DMF: elimination products are produced in high yields even from sterically hindered starting materials, and not only from halides, but also tosylates.

Numerous stable carbohydrate derivatives with an olefinic bond in their carbon skeleton are constituents of a series of naturally occurring compounds. Besides, these unsaturated carbohydrates represent a versatile family of chiral templates that can be further elaborated into useful synthons.[1]

The introduction of double bonds in the carbohydrate framework results in the formation of three categories of compounds: alkenes, enols and enediols. Furthermore, the double bond may be exo- or endocyclic with respect to the carbohydrate ring (furanoid or pyranoid). Their various versatile properties and syntheses are reported comprehensively in the literature.[1–3] The normal standard procedure for the synthesis of glycals and 2-hydroxyglucals is the elimination of HBr from acylglycosyl bromides by treatment with Zn/Cu in acetic acid, and its improved version[4] with secondary amines,[2a,4,5] and, more recently, with the dimeric Ti(III) species $(Cp_2TiCl)_2$[6a] or using sodium hydride in DMF.[6b] Much attention has been focused on the synthesis of 6-deoxyhex-5-enopyranose derivatives, due to their unique synthetic utility, and on their transformation to cyclohexane (cylitols) and cyclopentane derivatives in which the ring oxygen atom of the sugar is replaced by a methylene group.[7,8] The hex-5,6-enopyranosides, also starting materials for the synthesis of prostaglandins,[8a] are accessible by treating 6-bromo- and 6-iodo-6-deoxyhexopyranosides with NaH/DMF,[6] CsF/DMF,[9] AgF/pyridine,[10] 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)/CH_3CN,[11] NaI/BuNI/MS4A/DMSO and DBU/DMSO[12] or DBU/DMF.[13] These methods, however, often suffer from low yields or the formation of by-products.

Previously, we reported the cleavage of silyl ethers[14] with sodium hydride (NaH) in hexamethylphosphoric triamide (HMPA) and the selectivity of this reagent towards the cleavage of *tert*-butyldiphenylsilyl ethers in the presence of *tert*-butyldimethylsilyl ethers.[15] In an extension of our work on the reactivity of NaH in HMPA,[16] we exposed 6-*O*-*p*-tosylsulfonyl-3,4-di-*O*-acetyl-D-glucal (**1**) to our reagent with the intention of cleaving the tosyl group, but surprisingly found that 3,4-di-*O*-acetyl-5,6-enoglucal was formed as an elimination product in 90% yield (Scheme 1).

As shown in Table 1, our NaH/HMPA[16] reagent gives higher yields of elimination products compared to the reported NaH/DMF procedure,[6] and is also suitable for dehydrotosylations. Using NaH/DMF for entries 1, 7, 8 and 9 yielded less than 5% of the elimination products; in addition a complex mixture of non-separable side products was obtained. To determine the general utility of this reagent, we prepared several tosylates and halides of different sugars, reacted these with sodium hydride in HMPA and isolated the elimination products in excellent yields (Table 1).

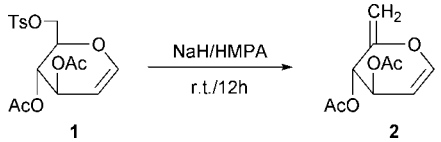
In conclusion, NaH in HMPA[16] is a reagent which produces elimination products from halides as well as *p*-toluenesulfonic acid esters in high yields. As this procedure has several advantages it is a valuable addition to existing methods.

Experimental

In a typical reaction, a solution of a halogenated or tosylated sugar (1 molar equiv.) in HMPA (1 ml per mmol; if the starting sugar is not soluble in HMPA, a saturated solution in THF can be added) to a suspension of oil-free NaH (2.2 molar equiv.) in anhydrous HMPA, (1 ml per mmol) under argon at 0 °C and the mixture allowed to stir at room temperature for the time given in Table 1. Upon completion of the reaction (TLC analysis, 12 to 24 h), quenching was performed either with wet diethyl ether or water and the mixture filtered through a pad of Celite. Aqueous work up of the filtrate and silica gel chromatography afforded pure elimination products (Table 1).[16]

Representative spectroscopic data for 2

$[\alpha]_D^{25} = -176°$ ($CHCl_3$, $c = 1$); ^1H NMR (300 MHz, $CDCl_3$): δ 6.54 (1H, dd, $J_{1,2} = 5.1$, $J_{1,3} = 0.6$, H-1), 5.42 (1H, dd,



1 **2**

Scheme 1

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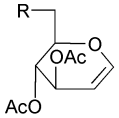
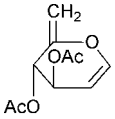
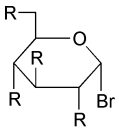
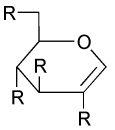
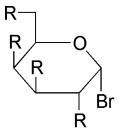
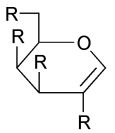
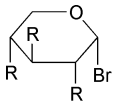
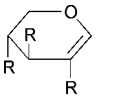
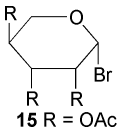
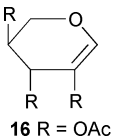
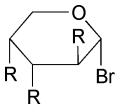
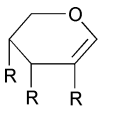
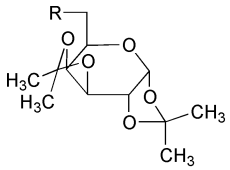
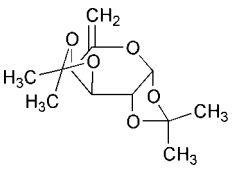
Table 1 Elimination of HX and HOTs with NaH in HMPA

Entry	Reactant	Product	Reaction time/h	Isolated yield (%)	Literature yield (%)	mp/°C	$[\alpha]_D^{25}$/°
1	 **1** R = OTs **3** R = Br **4** R = I	 **2**	12 13 12	90 96 97	73[17]	Oil	−176[a]
2	 **5** R = OAc **6** R = OBz	 **7** R = OAc **8** R = OBz	12 12	91 93	56,[18] 78[19] 53[20]	64–67 121–122	−21[a] −77[a]
3	 **9** R = OAc **10** R = OBz	 **11** R = OAc **12** R = OBz	12 12	88 90	89,[21a] 37[21b] 40,[22] 70[23]	110–111 Oil	−6[a] −52[b]
4	 **13** R = OAc	 **14** R = OAc	12	89	Ref. 16	81–82	−272[a]
5	 **15** R = OAc	 **16** R = OAc	18	91	Ref. 16	125–127	+282[a]
6	 **17** R = OAc	 **18** R = OAc	24	87	51[2c]	57–58	+205[a]
7	 **19** R = OTs **20** R = Br **21** R = I	 **22**	22	95	70,[6b] 68[24]	89–90	−135[b]

$J_{4,3}$ = 3.1, $J_{4,6'}$ = 1.7, H-4), 5.10 (1H, ddd, $J_{3,1}$ = 0.6, $J_{3,2}$ = 1.4, $J_{3,4}$ = 3.1, H-3), 5.08 (1H, dd, $J_{2,1}$ = 5.1, $J_{2,3}$ = 1.4, H-2), 4.91 (1H, d, $J_{6,6'}$ = 1.6, H-6), 4.65 (1H, dt, $J_{6',4}$ = 1.7, $J_{6',6}$ = 1.6 Hz, H-6′), 1.67 (s, 3H, CH_3CO), 1.66 (s, 3H, CH_3CO).

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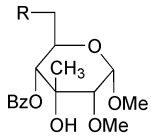
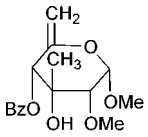
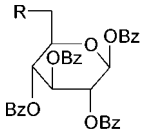
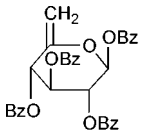
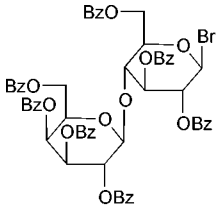
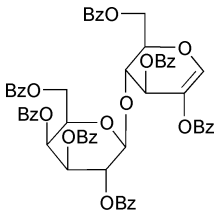
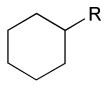
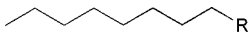
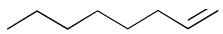
Table 1 Continued

Entry	Reactant	Product	Reaction time/h	Isolated yield (%)	Literature yield (%)	mp/°C	$[\alpha]_D^{25}$/°
8	 **23** R = OTs **24** R = Br **25** R = I	 **26**	17	90	77[25]	113–114	+121[a]
9	 **27** R = OTs **28** R = Br **29** R = I	 **30**	23	92	67[26]	131–132	−11[a]
10	 **31**	 **32**	16	97	67[3c]	93	+47[a]
11	 **33** R = OTs **34** R = I	 **35**	14 12	94 92	82[27]	Liquid	N/A[c]
12	 **36** R = OTs **37** R = I	 **38**	13 14	88 87	80[28]	Liquid	N/A[c]

[a] $CHCl_3$, $c = 1$. [b] Acetone, $c = 1$. [c] Not applicable.

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16 (*a*) All synthesized compounds were characterized by ^1H, ^{13}C NMR and mass spectrometry and gave satisfactory elemental analyses; (*b*) Pure compounds were collected after column chromatography, whereas compounds **35** and **38** were obtained after distillation of crude mixtures; (*c*) This is not an improvement in an existing method;[6b] rather, it is a new method for dehydrotosylation and dehydrohalogenation. Until now there was no existing method that could eliminate both HOTs and HX. Due to these elimination properties of a single reagent, the toxicity of HMPA could be compromised.

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