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Reductive Cleavage of Acetals and Ketals with 9-Borabicyclo[3.3.1]nonane†

John A. Soderquist,* Iveliz Kock, and Maria E. Estrella

University of Puerto Rico, Department of Chemistry, Rio Piedras, Puerto Rico 00931-3346

Abstract:

The reductive cleavage of benzaldehyde acetals and acetophenone ketals with the air-stable crystalline 9-borabicyclo[3.3.1]-nonane dimer provides monobenzylated ether derivatives of diols and 1,2-oxygen-transposed β-phenethyl alcohols, respectively. The boron moiety is effectively recovered through simple procedures which involve convenient air-stable reagents and boron byproducts. The process is particularly selective for 1,3-diols giving the more substituted monobenzyl ether derivatives exclusively. With acetophenone ketals both reduction and elimination occur, permitting 9-BBN-H to hydroborate the resulting styrene to produce 1,2-oxygen-transposed β-phenethyl alcohols cleanly. Potential applications of this new process were illustrated with the synthesis of the hallucinogen, mescaline, and the analgesic, ibufenac.

Introduction

Acetals and ketals have an extensive history as protecting groups for carbonyls and diols in organic synthesis.[1] This protection is commonly employed in the total synthesis of multifunctional compounds.[2] Normally stable to neutral and strongly basic conditions, it exhibits the lack of reactivity associated with ethers. In the absence of Lewis acids, acetals are insensitive to nucleophiles, making them excellent carbonyl protecting groups. However, if desired, Lewis acid-mediated additions to acetals can be highly useful synthetic processes.[3] For example, their reductive cleavage can be effected through many Lewis acid/hydride combinations such as $LiAlH_4/AlCl_3$, $LiAlH_4/BCl_3$ (including $BHCl_2$ or BBr_3), Me_3SiH/Me_3SiOTf, Et_3SiH/Nafion-H, $ZrCl_4/NaBH_4$, $NaBH_3$-CN/(HCl or BF_3), $Zn(BH_4)_2/Me_3SiCl$, BH_3·SMe_2/TMSOTf and BH_3·THF/ Bu_2BOTf.[4] This last combination provided the best results for the selective reductive ring opening of 4,6-*O*-benzylidene acetals of hexapyranosides to the corresponding 4-*O*-benzyl ethers.[4i,j] Moreover, these reductive processes have found applications in the synthesis of pharmaceuticals and other natural products.[4k,l]

The reduction of benzylidine acetals to ethers can also be viewed as a useful approach to the monobenzylation of diols.[5] Diisobutylaluminum hydride (DIBAL-H) has proven useful for cyclic benzylidene acetals,[5c] and with the benzyl group providing highly versatile alcohol protection, this methodology has been used in total synthesis.[6] This approach to the selective monoprotection of chemically similar diols is an important process. While the direct process commonly gives mixtures, several very creative methods have been developed for the selective benzylation of of 1,*n*-diols.[5c,7] However, the reductive cleavage of cyclic benzylidene acetals represents perhaps the most useful protective strategy for the synthesis of monobenzylated diols.[5c,6,8]

One other interesting feature of the selective monoprotection vs acetal reduction strategies for monoalkylated diols, is the selectivity of the process. The monoprotection of unsymmetrical diols favors the less hindered alcohol site.[9] On the other hand, the selective synthesis of the more

† This work is dedicated to my mentor, the late, great Professor Herbert C. Brown whose love of chemistry, standards of excellence, and levels of accomplishment have been profoundly influential and inspirational to me and many others. His passing marks the end of an era.

* To whom all correspondence should be addressed: E-mail: jas@janice.uprr.pr.

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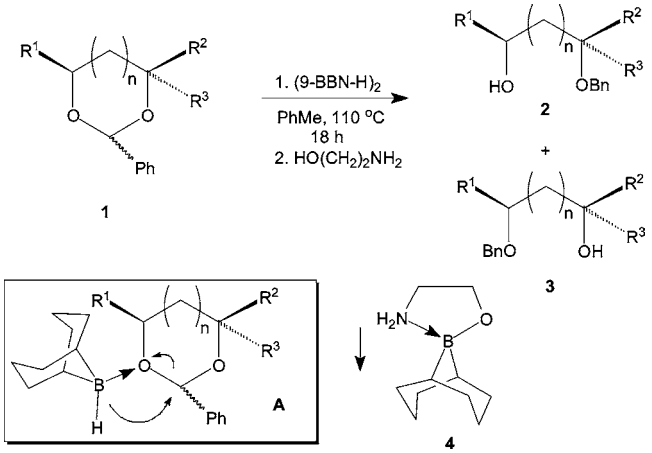
Scheme 1



hindered monoprotected diols are normally based upon the formation of cyclic intermediates.[10]

Consideration of the above reagents and combinations of reagents used for the reductive cleavage of acetals, none are air-stable reagents which can be conveniently weighed and used directly for this conversion. As a dialkylborane, 9-borabicyclo[3.3.1]nonane (BBN-H) is unrivaled in both stability and selectivity in a variety of reductive processes.[11] Recent developments include the reduction of tertiary amides to amines and the reduction of oxazolidines.[12] This thermally stable ring system also permits its derivatives to undergo many subsequent conversions with the 9-BBN moiety serving as spectator ligation. During the development of an effective scalable procedure for the preparation of 9-BBN-H dimer, we had observed that the reagent did react with acetals.[11a] This process was not explored in depth at the time. However, the above features of 9-BBN-H, together with its high Lewis acidity relative to that of other dialkylboranes, suggested that it may provide a particularly useful new reagent for the reductive cleavage of acetals and ketals and related processes.

Results and Discussion

Representative 1,3-dioxanes and dioxolanes were prepared by employing standard procedures. These were subjected to the reductive cleavage conditions developed for 9-BBN-H dimer (18 h, reflux temperature, toluene) (Scheme 1, Table 1). The course of the reaction is easily monitored by ^{11}B NMR with the borinic ester product exhibiting the characteristic signal at δ 55 which replaces the 9-BBN-H signal δ 27. The chemoselectivity of the process is excellent with only the dioxolane **1c** giving a detectable amount of the lesser substituted benzyl ether (**3c**, 30%). The products are easily isolated through a non-oxidative ethanolamine workup which forms **4** as an insoluble byproduct which is easily separated from **2**/**3** by filtration. In addition to the above 2-Ph derivatives, the more hindered 2-*tert*-butyl-1,3-dioxolane was also reductively converted to ethylene glycol mononeopentyl ether (71%). However, the process was slower (48 h, reflux) and incomplete (14% unreacted starting acetal). While 9-BBN-H is less reactive in this reductive cleavage than is DIBAL-H, it exhibits comparable selectivity and efficiency and is easier and safer to handle.

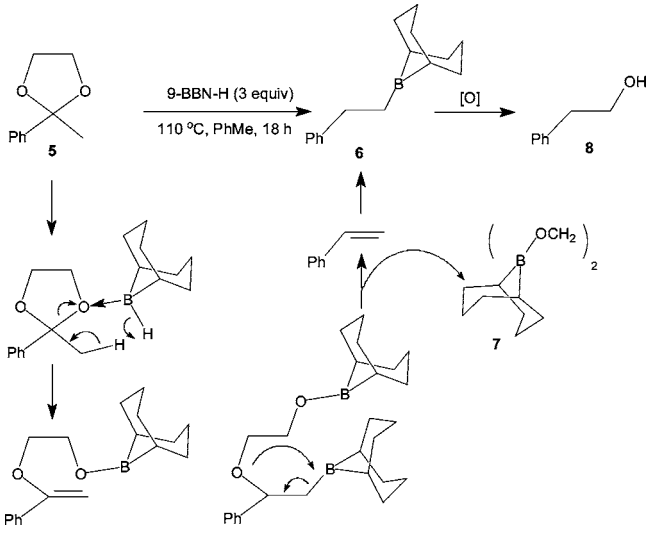
Table 1. **Reductive cleavage of cyclic acetals 1 with 9-BBN-H**

entry	n	R^1	R^2	R^3	yield % (2:3)
a	0	H	H	H	85
b	0	Me	Me	H	81[a]
c	0	Hx	H	H	77 (70:30)[b]
d	1	H	H	H	83
e	1	Me	H	H	83 (100:0)
f	1	Me	Me	Me	67 (100:0)

[a] The 2-Ph-3,5-diMe relationship in **1b** was *trans, cis* (60%) and *cis, cis* (40%). [b] For **1c**, *cis*/*trans* = 1.

The sensitivity of this process to steric factors suggested that the reduction of ketals with 9-BBN-H may be quite slow. This proved not to be the case with acetophenone ethylene glycol ketal (**5**) whose reduction (3.25 equiv of 9-BBN-H) in refluxing PhMe was complete in 18 h, but with the unexpected formation of what were ultimately identified as *B*-(β-phenylethyl)-9-BBN (**6**) and $(CH_2O\text{-}9\text{-}BBN)_2$ (**7**). This mixture was oxidized with alkaline hydrogen peroxide to provide **8** (73%). Under similar conditions, the acetophenone dimethoxy ketal also provides **8** (79%) (Scheme 2).

Scheme 2



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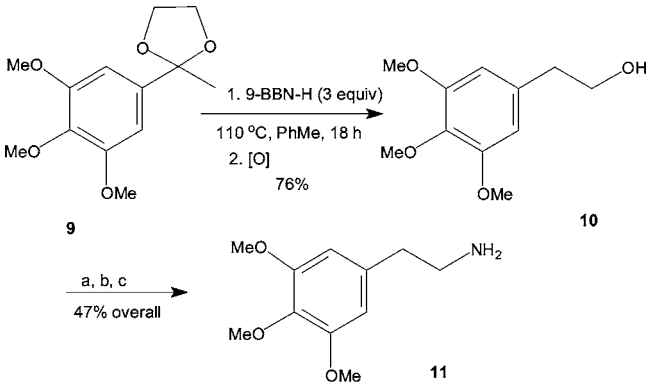
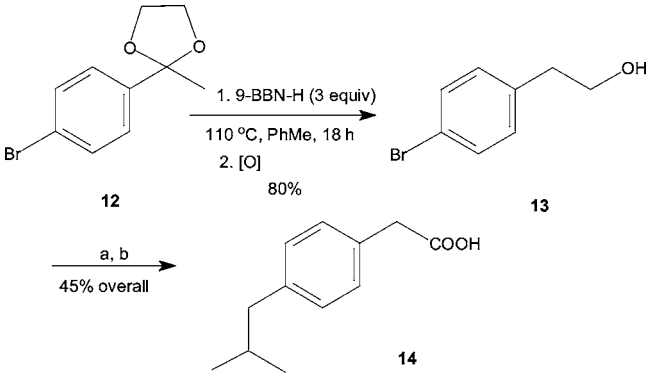
Scheme 3



[a] MsCl, TEA, CH_2Cl_2 [b] NaN_3, DMF, 90 °C [c] $LiAlH_4$, Et_2O

Scheme 4



[a] *i*-Bu-9-BBN, NaOH, $Pd[PPh_3]_4$ [b] TEMPO, $NaClO_2$, MeCN

We had originally noted by ^{11}B NMR analysis of the mixture obtained from the 1.25:1.00 9-BBN-H/**5** stoichiometry, that a borinic ester was accompanied by the slow evolution of a gas and the unexpected formation of a trialkylborane. The initial elimination was unexpected, but the *beta*-elimination of β-alkoxyalkyl-9-BBNs is common.[13] This overall process corresponds to a reductive 1,2-oxygen transposition which is new. For 1,3-dioxolanes derived from alkyl methyl ketones which contain α-hydrogens in the alkyl group, product mixtures were observed. However, to demonstrate its utility for acetophenone derivatives, we chose to develop this process through its application to the synthesis of the hallucinogen, mescaline (**11**) and to the analgesic, ibufenac (**14**) (Schemes 3 and 4).[14] These ketals (i.e., **9**, **12**) undergo the clean reductive 1,2-oxygen transpositions producing the corresponding β-phenethanols (i.e., **10**, **13**) efficiently. Standard procedures were used to convert these intermediates into the desired target compounds.[15]

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(15) An X-ray structure of **14** was obtained, and these data are included in the Supporting Information.

Conclusions

In summary, this work presents some new applications for the 9-borabicyclo[3.3.2]nonane dimer. The reduction of cyclic acetals for the chemical differentiation of equivalent hydroxyl groups in symmetrical diols has been demonstrated. The chemoselective protection of diols as their monobenzylated ether derivatives was also achieved with unsymmetrical diols. With acetophenone ketals, 9-BBN-H undergoes a novel reductive 1,2-oxygen transposition to provide the corresponding β-phenethyl alcohol derivatives. This last transformation was effectively applied to synthesis of mescaline and ibufenac.

Experimental Section

All experiments were carried out in predried glassware (1 h, 150 °C) under a nitrogen atmosphere. Standard handling techniques for air-sensitive compounds were employed for all the operations. Nuclear magnetic resonance (NMR) spectra were obtained using Bruker Avance DPX-300 and Bruker Avance DRX-500 spectrometers. Infrared spectra were recorded on a Bruker Tensor 27 FTIR spectrophotometer with HELIOS ATR attachment. Mass spectral data were obtained with a Hewlett-Packard 5995A GC/MS spectrometer (70 eV). Elemental analyses were performed by Atlantic Microlab, Norcross, Georgia. X-ray measurements were performed on a Bruker CCD diffractometer with graphite monochromated Mo Kα radiation. Crystalline 9-borabicyclo-[3.31]nonane dimer was either prepared[11] or obtained from Sigma Aldrich, Inc. The diols and other reagents used in this study were obtained from this supplier.

Representative Acetal Reductive Cleavage. 2-Benzyloxy-1-ethanol (2a).[16] To a flask containing 9-BBN-H (8.4 mmol, 1.03 g), were added **1a** (6.7 mmol, 1.03 g) and toluene (0.7 mL). The reaction mixture was refluxed under nitrogen atmosphere for 18 h. After cooling to room temperature, the reaction volume was doubled with pentane, and ethanolamine (8.4 mmol, 0.52 g) was added. The reaction was stirred at room temperature for 1 h, followed by the filtration of the white precipitate. The filtrate was concentrated under reduced pressure and distilled to afford 0.90 g (85%, bp 72−73 °C, 1 mmHg; lit.[15] bp 135 °C, 13 mmHg) of **2a**. ^1H NMR (300 MHz, $CDCl_3$) δ 3.58 (dd, 2H, J = 4.9, 4.3 Hz), 3.74 (dd, 2H, J = 4.9, 4.3 Hz), 4.55 (s, 2H), 7.35 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 61.7, 71.4, 73.2, 127.7, 127.7, 128.3, 137.8. IR (NaCl) 3400, 1450, 1355, 1105, 1060, 735, 695 cm^{-1}.

2-Phenylethanol (8) from 5.[17] To a flask containing 9-BBN-H (32.5 mmol, 3.97 g) were added **5** (10.0 mmol, 1.64 g) and toluene (1.0 mL). The reaction mixture was refluxed under nitrogen atmosphere (H_2 evolution) for 18 h. After cooling to room temperature, the **6**/**7** mixture (see SI) was oxidized with the addition of ethanol (5 mL) and NaOH solution (3 M, 12.5 mmol, 4.17 mL) followed by the dropwise addition of hydrogen peroxide solution (10 M, 37.5

(16) Eliel, E. L.; Badding, V. G.; Rerick, M. N. *J. Am. Chem Soc.* **1962**, *80*, 2371. CAS # 622-08-2.

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mmol, 3.75 mL). The mixture was refluxed for 2 h to destroy any remaining H_2O_2. After reaching room temperature, the reaction mixture was saturated with solid NaCl, extracted with ethyl ether (3 × 15 mL) and dried over anhydrous K_2CO_3. The solution was concentrated and purified by silica gel column chromatography to give 0.89 g (73%) of **8**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.74 (t, J = 6.7 Hz, 2 H), 3.70 (q, J = 5.9 Hz, 2 H), 4.55 (s, 1H), 7.13 (m, 3 H), 7.23 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.0, 63.4, 126.3, 128.4, 128.9, 138.5. IR (NaCl) 3348, 3028, 2941, 2878, 1045 cm^{-1}.

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Supporting Information Available

Experimental procedures, analytical data, and selected spectra for **1**−**3**, **5**, and **9**−**14** and X-ray data for **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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