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CHEMOSELECTIVE REDUCTIVE CLEAVAGE OF KETALS AND ACETALS

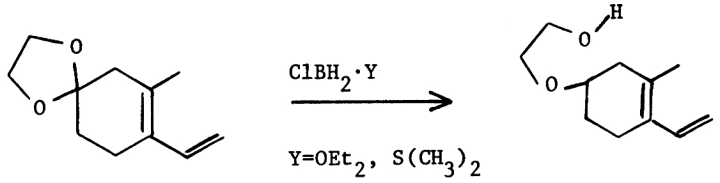
R. J. BORDERS and T. A. BRYSON*

Department of Chemistry, University of South Carolina,

Columbia, South Carolina 29208, U.S.A.

Utilization of complexed monochloroborane as a reducing agent for ketals and acetals is reported.

Reductive cleavage of acetals and ketals has been observed under a variety of conditions: lithium aluminum hydride-aluminum chloride mixtures,[1] treatment with trichloro-, dichloro-, and tribromo-borane followed by lithium aluminum hydride,[2] excess borane in tetrahydrofuran (BH_3·THF complex) employing long reaction times,[3,5] and dihydridoaluminum chloride (AlH_2Cl).[4] Clearly these conditions are relatively non-chemoselective, restricting use of such procedures. Herein is reported the use of monochloroborane etherate ($ClBH_2$·OEt_2)[6] as a mild, selective ketal and acetal reductive cleavage reagent. Functionality other than the ketal or acetal affected by strong Lewis acids or active hydrides can be present when using this reagent.



1 2

Initially, $ClBH_2$,[6,7] (etherate or dimethyl sulfide complex), was observed to react with diene ketal 1 to yield hydroxyether 2, with no diene hydroboration (oxidation) products detected.[13] The observed chemoselectivity of $ClBH_2$ for "reduction" of the ketal protecting group in the presence of a diene that has been shown in this laboratory to be reactive toward other hydroborating reagents (9BBN, thexylborane) suggested further studies. Additional substrates 3-10 were prepared using standard procedures for acetal/ketal formation. All substrates were purified by chromatography (Waters Prep LC/system 500A). This same selectivity was observed for

cyclic ketals of differing ring size, cyclic ketals containing a geminal dimethyl group, acyclic ketals and acetals. Reduction of ketals (acetals) to the exclusion of reaction with olefins of various substitution patterns, dienes and conjugated esters has considerable potential synthetically, (Table 1).

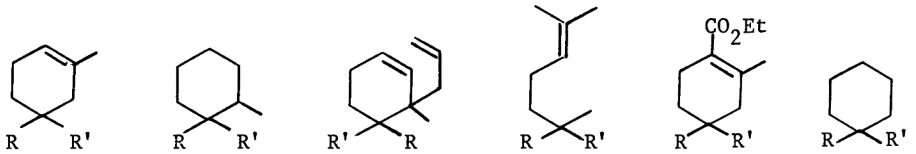
Typically, 1 eqviv. of $ClBH_2 \cdot OEt_2$ in ether was added dropwise to a magnetically stirred etheral solution of diene at 0 °C (under Ar). After 1 h at 0 °C the reaction was quenched with an ethanolic sodium hydroxide/hydrogen peroxide mixture followed by the usual workup and purification. Hydrogen peroxide is not necessary in this workup but was routinely used to assess the extent (if any) of competing hydroboration. In experiments without hydrogen peroxide purification was more difficult and the yields were generally lower (2-3%).

Table 1. Ketal Reduction

Starting material	Product	$H_2BCl \cdot OEt_2$ % Yield[a,b]	Recovered SM $H_2BCl \cdot OEt_2$(%)	$H_2BCl \cdot SMe_2$ % Yield[a,b]	Recovered SM $H_2BCl \cdot OEt_2$(%)
1	2	80	(12)	45	(44)
3a	3f	88	--	40	(48)
4a	4f	87	(7)	60	(33)
5a	5f	82	(12)	50	(30)
6a	6f	83	(7)	0	(--)
6a	10	0	(--)	83	(10)
6d	6h	75	(15)	60	(28)
7a	7f	83	(10)	42	(48)
7c	7g	85	(8)	50	(42)
7e	7j	65	(--)	(--)	(--)
8b	8h	90	(--)	64	(24)

a) Isolated yield average of two or more reactions, product yields are not based on recovered starting material.

b) All products exhibit IR, NMR, and M/S in accordance with theory.



3 4 5 6 7 8

a R,R' = $-O(CH_2)_2O-$

b R,R' = $-O(CH_2)_4O-$

c R,R' = $-OCH_2C(CH_3)_2CH_2O-$

d R,R' = $-OEt$

e R,R' = $-O\underset{CH_3}{CH}-\underset{CH_3}{CHO}-$

f R,R' = $-H, -O(CH_2)_2OH$

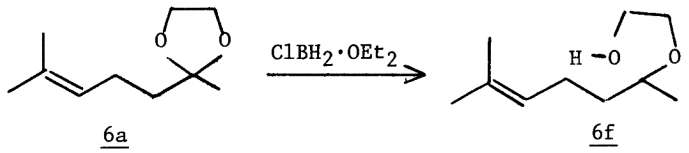
g R,R' = $-H, -OCH_2C(CH_3)_2CH_2-OH$

h R,R' = $-H, -OEt$

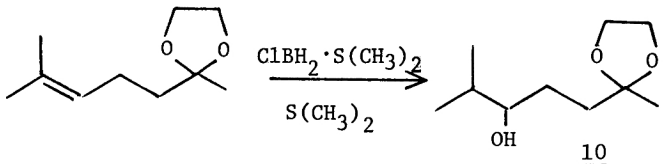
i R,R' = $-H, -O(CH_2)_4-OH$

j R,R' = $-H, -O\underset{CH_3}{CH}\underset{CH_3}{CH}-OH$

Monochloroborane dimethylsulfide complex[7] gave the same results as the etherate complex with cyclic compounds containing ketals although in reduced yields (Table 1). However, an interesting reversal of the chemoselectivity was observed for aliphatic ketal 6a. Using $ClBH_2 \cdot SMe_2$ normal hydroboration was observed affording 10, while $ClBH_2 \cdot OEt_2$ yielded the hydroxyether 6f.



6a 6f



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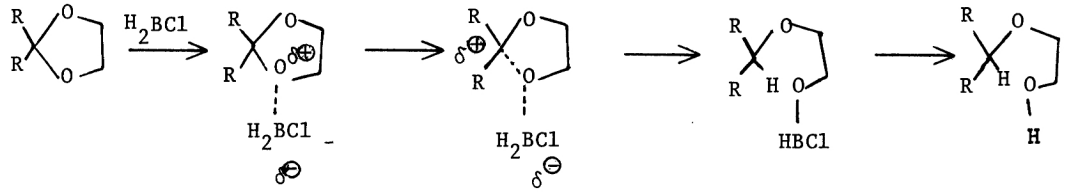
Based on the reversal of chemoselectivity with 6a and the dimethyl sulfide complex, the reactions of Table 1 were repeated using an additional equivalent of dimethylsulfide followed by an equivalent of $H_2BCl \cdot SMe_2$ with the expectation of supressing the ketal reduction and altering the reaction toward normal hydroboration. However, ketal cleavage was observed with, at best, only minor amounts of hydroboration products under these conditions, as was the case when two equivalents of dimethylsulfide were employed. Excess dimethylsulfide did cause the production of several minor by-products (via TLC). However, these minor by-products were not further characterized since the major product was dioxolane cleavage along with varying amounts of recovered starting material. When $ClBH_2 \cdot OEt_2$ was reacted with 1,2-methylenedioxybenzene no reaction occurred. This result could be attributed to lower basicity of the aromatic acetal oxygens or that the lone pair orbitals of oxygen are not orientated properly to complex with boron.[10]

This reduction process is presumably initiated by formation of a Lewis-acid base complex of monochloroborane and the appropriate ketal or acetal. Opening of this adduct would be closely followed by reduction.



Precedence for this type of cyclic intermediate is well documented.[3,4,8] This boron com-

plexing phenomena may account for the generally reduced yields when employing the sulfide complex since the sulfur boron complex is considered to be stronger[11,12] and therefore less reactive than the ether complex. The recent report by Brown[9] emphasized the chelation of ester oxygens with borane and the tighter coordination of borane dimethylsulfide. The reaction sequence and the lower yields of hydroxyethers when using $ClBH_2 \cdot SMe_2$ are in accordance with his suggestions. Additional reagent selectivities and the reversal of this process employing excess sulfide with ketal is being further explored in hopes of gaining more insight into this "protecting group" reduction process.

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