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An efficient protection of carbonyls and deprotection of acetals using decaborane

Seung Hwan Lee, Ji Hee Lee and Cheol Min Yoon*

Graduate School of Biotechnology, Korea University, Seoul, South Korea

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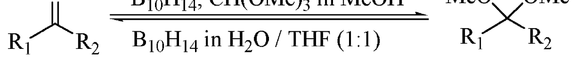
Abstract—Carbonyls were efficiently converted to the corresponding dimethyl acetals at room temperature using trimethyl orthoformate and 1 mol% of decaborane under a nitrogen atmosphere. In turn, acetals were deprotected to the corresponding carbonyls using 1 mol% of decaborane in aqueous THF chemoselectively. © 2002 Elsevier Science Ltd. All rights reserved.

Protection of carbonyls and deprotection of acetals (or ketals) are two of the most important reactions in organic chemistry and many methods have been developed for these reactions.[1] Although a lot of conventional catalysts including acid catalysts[1,2] and $Sc(NTf)_3$[3] have been reported for the protection of carbonyls into dimethyl acetals, the search for a new catalyst is still actively pursued due to the problems such as difficulty in handling the reagent, poor chemoselectivity and limited examples.[3] For deprotection of dimethyl acetals into carbonyls, many acid catalysts such as protic and Lewis acid catalysts have been developed.[1,4] However, many of these methods involve the use of corrosive reagents and elevated temperature. Several mild methods have also been developed for the conversion of acetals and ketals into carbonyls.[5] Although a selective method[6] has also been reported, a mild and neutral method which would effect the selective cleavage of acetals (or ketals) is still required.

Decaborane[7] is a commercially available white solid that decomposes slowly in air. Typical known reactions of decaborane include adduct formation and *ortho*-carborane[8] preparation for BNCT. Decaborane as a reducing reagent in organic synthesis has been reported, but was inefficient due to its low reactivity in hexane even at high temperature.[9] By changing the solvent system to protic solvents, the reducing power of decaborane was increased to be efficient for reductive etherification and reductive amination.[10] As a result of an ongoing study, decaborane was found to be a mild, chemoselective and efficient Lewis acid catalyst in the conversions between carbonyls and acetals. Here, we wish to describe the protection of carbonyls to acetals and the deprotection of acetals to carbonyls using a catalytic amount of decaborane (Scheme 1).

Various aldehydes and ketones were efficiently converted to the corresponding dimethyl acetals in the presence of trimethyl orthoformate using a catalytic amount of decaborane in anhydrous methanol at room temperature under a nitrogen atmosphere and the results are shown in Table 1.[14] Yields of these reactions are almost quantitative in most cases. Decaborane (1 mol%) was used in all of the cases except for acetophenone (2 mol% decaborane). The reaction seemed to proceed through an oxonium ion intermediate (Scheme 2). The formation of any side product resulting from reduction of carbonyls[10c,d] and reductive etherification[10b] was not observed probably because acetalization might be much faster than the two reactions. Even if 30 mol% of decaborane was used, any other product related to reductive etherification and reduction of carbonyls was not formed at all. Decaborane (and/or its decomposed intermediate) as a Lewis acid catalyst might activate the carbonyl group via coordination and make the oxygen of the hemiacetal a good leaving group. Decaborane decomposes slowly in methanol. It is not clear at this moment whether all kinds of decomposed species of decaborane in addition



Scheme 1.

Keywords: carbonyls; acetals; protection; decaborane; chemoselective.

* Corresponding author. Fax: +82-2-3290-3433; e-mail: cmyoon@korea.ac.kr

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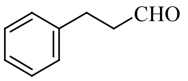
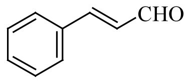
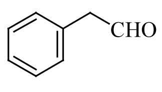
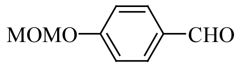
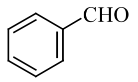
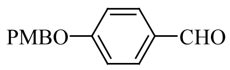
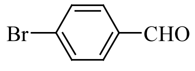
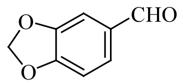
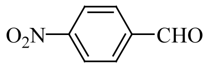
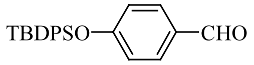
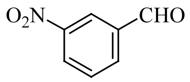
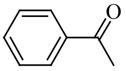
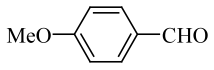
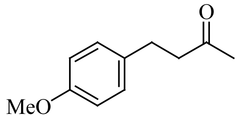
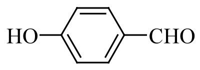
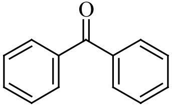
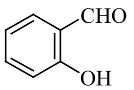
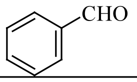
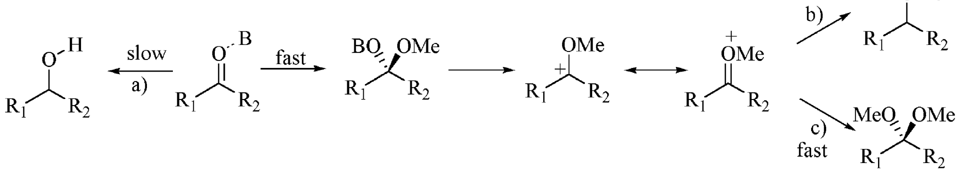
Table 1. Acetalization of carbonyls to acetals using decaborane in methanol

Entry	Substrate	Time (min)	Yield[a] (%)	Entry	Substrate	Time (min)	Yield[a] (%)
1		20	95	10		1	92
2		20	93	11		4	98
3		5	92	12[b]		5	95
4		15	99	13		4	94
5		120	96	14		10	98
6		120	92	15[c]		120	98
7		3	92	16		20	98
8		4	85	17		·	No rex
9		4	99	18		30	96[d]

a) Isolated yields. b) Ethyl acetate was used as a cosolvent to dissolve starting material. c) 2 mol% of decaborane was used. d) Product is benzaldehyde diethylacetal.

to decaborane have a catalytic activity or not,[11] but it is under investigation. Trimethyl orthoformate (3 equiv.) is a water scavenger that shifts the equilibrium to the side of the products. The several acid-sensitive functionalities such as MOM (entry 11), PMB (entry 12), methylenedioxy (entry 13) and TBDPS (entry 14) remained intact under our reaction conditions. It has been reported that the electron-withdrawing substituents at the alpha position to the carbonyl enhance the rate of acetal formation and electron donating groups (such as phenyl or conjugated) and retard acetal formation under acid-catalytic conditions.[12] However, under our conditions, aromatic aldehydes with electron donating groups (entries 7–9 and 11–14) and conjugated aldehyde (entry 10) were converted to dimethyl acetal within a few minutes. Dimethyl acetalization of aromatic aldehydes with a nitro group (known as an activating group for the acetal formation reaction) at *meta* or *para* positions (entries 5 and 6) and acetophenone (entry 15) was relatively slow. This result might be evidence that the oxonium ion generation step from carbonyl is a slow process as shown in Scheme 2. The oxonium ion generated from the benzaldehyde with the electron withdrawing group is quite unstable and results in a slow process for the formation of acetals. The acetophenone acetal formation is slow because hemiacetal formation is a slow process resulting from the steric hindrance to the methanol approach. The



a) Reduction b) Reductive etherification c) Acetal formation, B = $B_{10}H_{14}$ or its decomposed intermediates

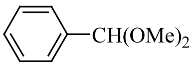
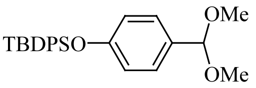
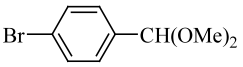
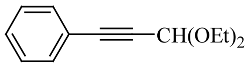
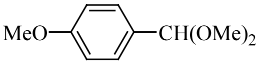
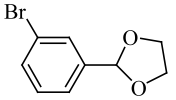
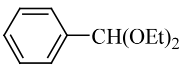
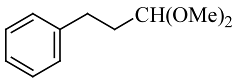
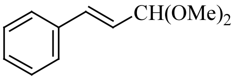
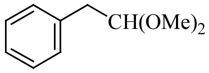
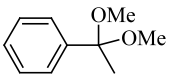
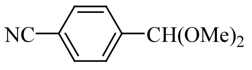
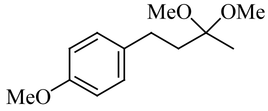
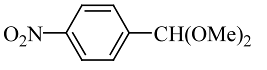
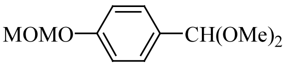
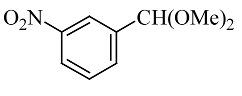
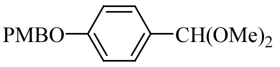
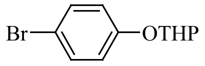
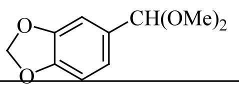
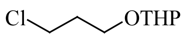
Scheme 2.

electron donating group stabilized the oxonium ion, helping it to form fast and thus increased the reaction rate. The benzophenone (entry 17) was not acetalized at all under our conditions. Our method is also effective for the preparation of diethyl acetal of carbonyls. The treatment of benzaldehyde with 3 equiv. of triethyl orthoformate in absolute ethanol using 1 mol% of decaborane gave diethyl acetal in 96% isolated yield (entry 18).

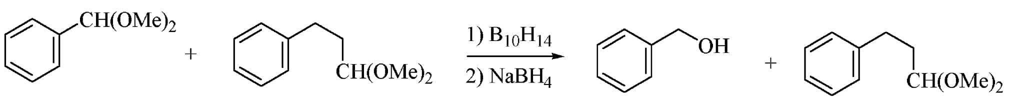
The acetals and ketals in aqueous THF using decaborane were deprotected to give the corresponding carbonyls and the results are shown in Table 2.[15] The experiment was conducted in a solution of water and tetrahydrofuran (1:1) in the presence of decaborane (1 mol%). Dimethyl acetals of aromatic aldehydes (entries 1–4) and conjugated aldehyde (entry 5) underwent smooth deprotection at room temperature in a relatively fast rate to give the corresponding aldehydes in high yields. Ketals of aromatic ketone (entry 6) and aliphatic ketone (entry 7) are efficiently deprotected to give ketones under these conditions. However, conjugation with a triple bond did not assist the deprotection of aldehyde acetals. When the diethyl acetal conjugated by a triple bond (entry 12) was subjected to the reaction conditions, no aldehyde was formed even after 6 h stirring at reflux. No reaction was observed with the cyclic acetal of 3-bromobenzaldehyde (entry 13) and the starting material was recovered quantitatively after 2 h stirring at rt. Acetals of nonconjugated aldehyde (entries 14 and 15) and benzaldehyde acetals with an electron withdrawing group such as cyano (entry 16) or nitro (entries 17 and 18) were resistant against deprotection under these conditions. The deprotection of these acetals did not proceed at all and substrates were recovered completely. Benzaldehyde dimethyl acetals were cleaved selectively in the presence of other acid labile protecting groups such as MOM (entry 8), PMB (entry 9), methylenedioxy (entry 10) and TBDPS (entry 11). THP ether of phenol and aliphatic alcohol survived under our reaction conditions within 6 h (entries 19 and 20).

Deprotection can apply to the selective reduction of carbonyls[13] by coupling with reduction in a consecutive way and one example is shown in Scheme 3. A solution of dimethyl acetal of benzaldehyde and hydrocinnamaldehyde in the presence of 1 mol% of decaborane

Table 2. Hydrolysis of acetals to carbonyls using decaborane in aqueous THF

Entry	Substrate	Time (min)	Yield[a)] (%)	Entry	Substrate	Time (min)	Yield[a)] (%)
1		2	94	11		5	91
2		1	99	12[b)]		6 h	No rex
3		4	92	13		2 h	No rex
4		10	84	14		6 h	No rex
5		30	99	15		6 h	No rex
6		1	92	16		24 h	No rex
7		5	99	17		24 h	No rex
8		5	96	18		24 h	No rex
9		20	96	19		6 h	No rex
10		10	99	20		6 h	No rex

a) Isolated yields. b) No reaction after 6 h reflux.



Scheme 3.

in aqueous THF was stirred for 10 min and then 1 equiv. of sodium borohydride was added. The reaction was monitored by TLC using a solution of ethyl acetate and hexane (1:10). After 10 min stirring at rt and the usual work-up followed by column chromatography, benzyl alcohol was obtained in 94% isolated yield and hydrocinnamaldehyde dimethyl acetal was recovered intact in 91% yield.

In conclusion, the carbonyls were efficiently converted to the corresponding dimethyl acetals at room temperature using trimethyl orthoformate as a water scavenger and decaborane as a Lewis acid catalyst under a nitrogen atmosphere. The advantage of this methodology is that it is simple, mild and efficient. Acetals and ketals were efficiently deprotected to the corresponding carbonyls using a catalytic amount of decaborane in aqueous THF. The deprotection condition is chemoselective against aliphatic and cyclic acetals, and acid labile protecting groups such as THP, TBDPS and MOM.

Acknowledgements

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14. *Typical procedure for dimethyl acetalization of carbonyl*: To a solution of benzaldehyde (100 mg, 0.942 mmol) and trimethyl orthoformate (0.3 ml, 2.827 mmol) in anhydrous methanol (4.7 ml) was added decaborane (1.2 mg, 1 mol%) and the resulting solution was stirred at room temperature under nitrogen. The reaction was monitored by TLC (ethyl acetate: *n*-hexane = 1:4). After 5 min, the reaction was quenched by adding saturated aqueous K_2CO_3 (10 ml) and extracted with methylene chloride (10 ml×3). Then, the organic layer was washed with water followed by saturated NaCl solution and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give benzaldehyde dimethylacetal as a colorless liquid in high yield (92%).

15. *Typical experimental for deprotection of acetal*: To a solution of benzaldehyde dimethyl acetal (0.2 ml, 1.31 mmol) in a solution of THF and water (1:1, 0.2 M) was added decaborane (1.6 mg, 1 mol%). The reaction was monitored by TLC using a solution of ethyl acetate and *n*-hexane (1:4). After 2 min stirring at rt, the reaction mixture was quenched with saturated sodium bicarbonate solution (5 ml), and extracted with ethyl acetate (10 ml). The organic layer was washed with water (10 ml×3) and dried over anhydrous magnesium sulfate. After concentration followed by column chromatography on a short silica gel pad using a solution of ethyl acetate and hexane (1:10), benzaldehyde was obtained in 94% yield.