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Selective reductions with complex hydride reducing agents

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Abstract - This paper describes the selective reductions with thioborane derivatives, zinc-modified cyanoborohydride, and the ate complex from diisobutylaluminum hydride and n-butyllithium. Reaction of carboxylic acids with 1,3,2-dithiaborinane in the presence of stannous chloride or boron trifluoride etherate in tetrahydrofuran gives 1,3-dithianes in high yields. The reaction of acids with thexylphenylthioborane in dichloromethane gives S,S'-diphenyl acetals, whereas esters are converted into phenyl sulfides in the presence of zinc iodide. Zinc-modified cyanoborohydride in ether selectively reduces allylic, benzylic, tertiary alkyl halides without reducing primary and secondary alkyl, vinyl, and aryl halides. Furthermore, the reagent in ether reduces aldehydes, ketones, and acid chlorides to alcohols and the reagent in methanol is very effective in the reduction of enamines, reductive amination of aldehydes and ketones, and deoxygenation of aldehdyes and ketones. The ate complex from diisobutylaluminum hydride and n-butyllithium, capable of reducing most reducible functional groups, is found to be a highly selective reducing agent. The reagent rapidly reduces simple primary alkyl bromides, benzylic, and allylic halides but slowly primary alkyl chlorides and secondary alkyl bromides. Tertiary amides are cleanly reduced to aldehydes and various selective reductions can be achieved by the use of the reagent.

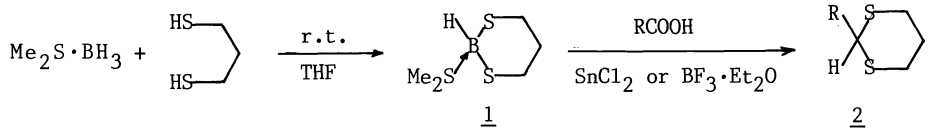
INTRODUCTION

The development of numerous selective reducing agents, capable of reducing a certain functional group in the presence of various other reducible functional groups has attracted a great deal of recent attention (ref. 1). In general, selective reducing agents have been prepared by modifying the steric and electronic effects of substituents on the boron atom or the aluminum atom. For instance, sodium cyanoborohydride containing a strong electron withdrawing cyano group is a milder and more selective reducing agent than sodium borohydride (ref. 2), whereas lithium tri-sec-butylborohydride having sterically bulky three sec-butyl groups is a stronger and highly stereoselective reducing agent than lithium borohydride (ref. 3). As our continuous efforts toward the development of new hydride reducing agents, we have recently developed new types of hydride reducing agents, namely 1,3,2-dithiaborinane and thexylphenylthioborane, which are capable of transferring hydride and mercapto moities to carboxylic acids by one step procedure (refs. 4 and 5). We have further modified the reducing properties of sodium cyanoborohydride by the addition of metal salts, especially zinc chloride (refs. 6 and 7). Finally, we have investigated the reducing properties of the ate complex generated from diisobutylaluminum hydride (Dibah) and n-butyllithium and found that the reagent is a powerful and highly selective reducing agent for the reduction of various functional groups (ref. 8).

1,3,2-DITHIABORINANE AND THEXYLPHENYLTHIOBORANE

A new method for direct conversion of carboxylic acids into synthetically useful thioacetals consists of the sequence of two steps, partial reduction of acids to the aldehyde stage (ref. 9) and the subsequent protection as thioacetals (ref. 10). As far as we are aware, this is the first example among various partial reductions using various complex hydride reducing agents where partial reduction and subsequent protection are achieved by one step procedure.

1,3,2-Dithiaborinane(1) was readily prepared by treating borane-dimethyl sulfide with 1 equiv of 1,3-propanedithiol in tetrahydrofuran and subsequent stirring at room temperature for a week (eq. 1). The ^{11}BNMR spectrum of the reagent (1) exhibited a doublet (J_{B-H}=160 Hz) at 62.4 ppm relative to boron trifluoride etherate. Reaction of phenylacetic acid with 2 equiv of the reagent (1) in tetrahydrofuran at room temperature gave a 60:25 mixture of benzyl 1,3-



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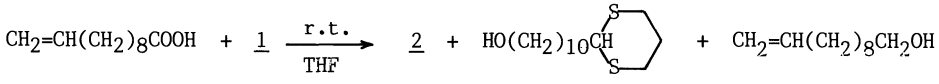
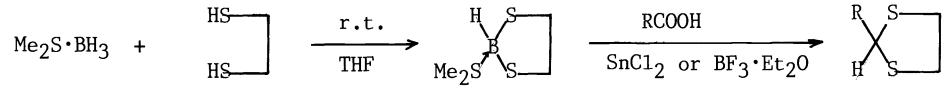


no additive:	44%	11%	8%
$BF_3 \cdot Et_2O$:	38%	13%	7%
$SnCl_2$:	78%		

(2)

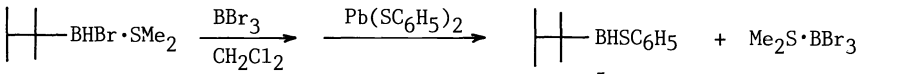
dithiane and phenethyl alcohol along with a small amount of several unidentified byproducts. Encouraged by this result, we have investigated the present reaction in detail. After much experimentation to find an optimum condition, several important observations have been made. First, the addition of stannous chloride or boron trifluoride etherate is very effective for clean conversion of acids into 1,3-dithianes (2) without accompanying alcohols (eq. 1). Secondary, even more important is the observation that acids can be selectively converted into 1,3-dithianes in the presence of alkenes using stanous chloride as an additive (eq. 2), although it has been reported that 1,3,2-dithiaborolane hydroborates readily alkenes (ref. 11). The use of boron trifluoride etherate was not effective for this purpose. Thirdly, 2 equiv of the reagent is not essentially required for this facile conversion. The best condition found for maximum yield and functional group selectivity are to employ 1.7 equiv of the reagent (1) and 1 equiv of stannous chloride or boron trifluoride etherate for each mole of aliphatic carboxylic acids in tetrahydrofuran at room temperature. In the case of aromatic acids, the use of 2 equiv of the reagent is recommended to obtain better yields. Carboxylic acids containing a bromo, an ester, and a tert-amide group were cleanly converted into the corresponding 1,3-dithianes without attacking such reducible groups by the reagent(1). As shown in Table 1, various carboxylic acids including sterically hindered acids were cleanly converted into the corresponding 1,3-dithianes (2) in high yields.



(3)

3 4

Furthermore, we have found that 1,3,2-Dithiaborolane (3), prepared by the reaction of borane-dimethyl sulfide with 1 equiv of 1,2-ethanedithiol in tetrahydrofuran at room temperature for 24 h, was capable of converting acids into 1,3-dithiolanes (4) in the presence of stannous chloride or boron trifluoride etherate (eq. 3). In general, the efficiency, applicability, and scope of this method were similar to those of using 1,3,2-dithioborinane (1).



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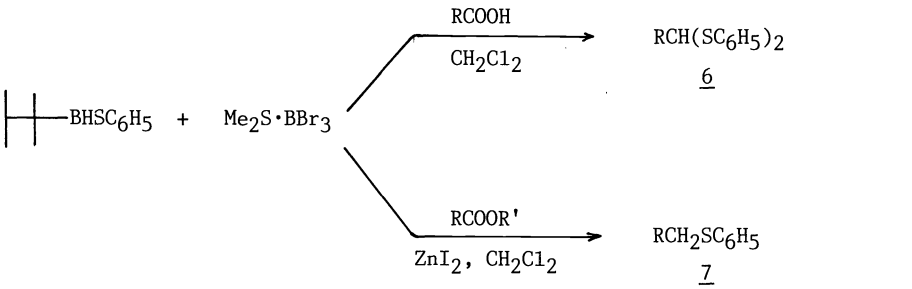


(5)

6

(6)

7

R'=Me, Et, i-C_3H_7, $CH_2C_6H_5$

Table 1. Direct Conversion of Carboxylic Acids to Thioacetals.

acid	time, h	isolated yields of 1,3-dithianes, %[a]	time, h	isolated yields of S,S'-diphenyl acetals, %[b]
$C_6H_5CH_2COOH$	5	84	2	81
$CH_3(CH_2)_5COOH$	3.5	90	4	87
$(CH_3)_2CHCOOH$	5	81	4	87
cyclohexanecarboxylic	3.5	82	3	84
1-adamantanecarboxylic	6	80	5	87
$Br(CH_2)_{10}COOH$	9	82	5	87
$HOOC(CH_2)_4COOMe$	12	83	3	82
C_6H_5COOH	20	74	7	71(14)[c]
p-Cl-C_6H_4COOH	20	71	6	75(14)[c]
p-MeO-C_6H_4COOH	20	75		

[a]The reaction was carried out with 1.7 equiv of the reagent (1) for aliphatic acids and 2.0 equiv for aromatic acids in the presence of 1.0 equiv of stannous chloride in tetrahydrofuran at room temperature.
[b]The reaction was carried out with 2.2. equiv of the reagent (5) in dichloromethane at room temperature.
[c]The numbers in parentheses indicate the isolated yields of benzyl phenyl sulfide and p-chlorobenzyl phenyl sulfide, respectively.

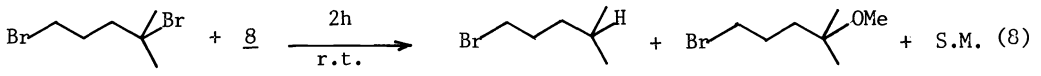
Although it has been reported the aryl- and alkylthioboranes hydroborate alkenes and reduce acids, aldehydes, and ketones to alcohols, their synthetic utilities have been hampered due to the facile cleavage of etheral solvents (ref. 12). We have found that thexylphenylthioborane (eq. 4), prepared from thexylbromoborane and bis(phenylthio) lead in dichloromethane, was also effective for conversion of acids into S,S'-diphenyl acetals (6) (eq. 5). The reaction was carried out with 2.2 equiv of the reagent (5) in dichloromethane at room temperature. As shown in Table 1, various structurally different acids were cleanly converted into S,S'-diphenyl acetals (6) in high yields. However, in the case of aromatic acids, small amounts of the corresponding phenyl sulfides were formed as a byproduct.

Since carboxylic esters were generally inert to the reagent (5), we considered the possibility of activating the carbonyl group of an ester by the addition of Lewis acids. Among several Lewis acids tested in this study, the use of 1 equiv of zinc iodide gave the best result for clean conversion of acids into phenyl sulfides (7) (eq. 6). The present method can be successfully applied to the preparation of various phenyl sulfides from various esters such as methyl, ethyl, benzyl, and isopropyl ester.

ZINC-MODIFIED CYANOBOROHYDRIDE

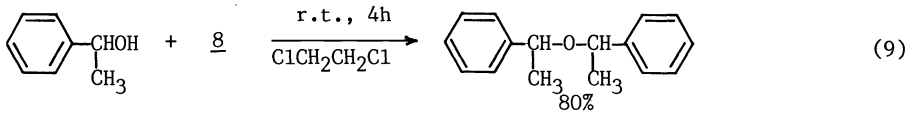
Although the reducing properties of sodium borohydride/metal salts have been intensively investigated (ref. 13), there are relatively few reports in the literature on the use of sodium cyanoborohydride/metal salts. It has been reported that the combination of socium cyanoborhydirde with Cu(II) and triphenylphosphine (ref. 14) and Pd(0) (ref. 15) reduces acid chlorides to aldehydes and allylic acetates to alkenes, respectively. We have also studied reducing properties of sodium cyanoborohydride/metal salts to modify the usual reducing ability of sodium cyanoborohydride alone. Among several metal salts such as zinc chloride, cobalt (II) chloride, stannous chloride, stannic chloride, and titanium chloride tested in this study, zinc chloride gave the promising results. Thus, we have investigated the reducing properties of sodium cyanoborohydride and zinc chloride in detail.

$$2\ NaBH_3CN + ZnCl_2 \longrightarrow \underset{\underline{8}}{\text{Zinc-modified Cyanoborohydride}} \qquad (7)$$



Et_2O:	95	0	0
DME:	10	0	82
MeOH:	10	58	25

Zinc-modified cyanoborohydride (8) utilized in this study was prepared by mixing sodium cyanoborohydride and zinc chloride in a 2:1 molar ratio at room temperature in several solvents such as ethyl ether, tetrahydrofuran, and methanol (eq. 7). The reagent (8) was relatively stable in aqueous media and its stability in aqueous media may enhance its utility as a versatile reducing agent, while zinc borohydride decomposes rapidly with evolution of hydrogen gas in alcoholic solvents. It was found that the reagent (8) in ether reduced allylic, benzylic, and tertiary halides to the corresponding alkanes without attacking primary and secondary alkyl, vinyl, and aryl halides. As shown in eq. 8, the tertiary bromide was cleanly and selectively reduced in the presence of the primary alkyl bromide in ether, whereas methyl ether was obtained as a major product in methanol. Similarly, selective reduction of tertiary, benzylic, and allylic halides can be achieved with zinc borohydride in ether (ref. 16) and sodium cyanoborohydride/stannous chloride (ref. 17). It is assumed that benzylic, allylic, and tertiary halides and alcohols are activated by zinc halides to generate carbocationic species which are trapped with various soft nucleophiles such as thiol, thioacids, and selenols (refs. 18 and 19).



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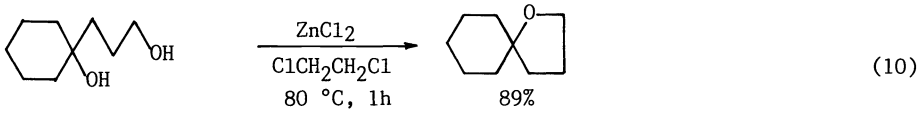
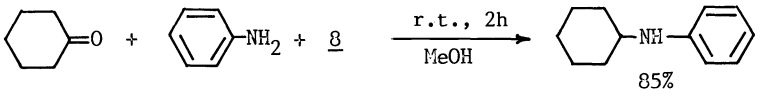


(10)

On the basis of this concept, we attempted deoxygenation of allylic, benzylic, and tertiary alcohols with the reagent (8) in ether or dichloroethane. However, reaction of α-methylbenzyl alcohol with the reagent (8) in dichloroethane at room temperature gave bis (α-methylbenzyl) ether in 80% yield (eq. 9). This result is in marked contrast with recently reported deoxygenation of benzylic alcohols with sodium cyanoborohydride/zinc iodide (ref. 20). We have developed a new convenient method for direct synthesis of ethers via zinc chloride mediated etherification of benzylic, allylic, and tertiary alcohols (eq. 9 and 10) (ref. 21).

Zinc-modified cyanoborohydride (8) in ether reduced aldehydes, ketones, and acid chlorides to alcohols but did not reduce acid anhydrides, acids, esters, and amides. The reagent in methanol did not readily reduce aldehyes and ketones, though the use of an excess amount of zinc chloride resulted in almost completion of the reduction. The reduction of enamines with the reagent (8) in methanol proceeded smoothly and the reaction was normally complete within 1 h at room temperature. Since the reduction of enamines with the reagent in methanol occurred much more rapidly than that of aldehydes and ketones, it was expected that reductive amination of aldehdyes and ketones (eq. 11) and reductive methylation of amines (eq. 12) could be effected by simply reacting the carbonyl compounds with amines by the use of the reagent (8) in methanol. It is of interest to note that the present procedure does not require pH control. Furthermore, the reductive deoxygenation of aldehydes and ketones via the intermediacy of tosylhydrazones was accomplished with the reagent in methanol at reflux (eq. 13).



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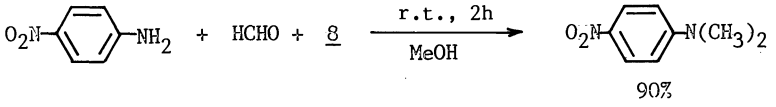

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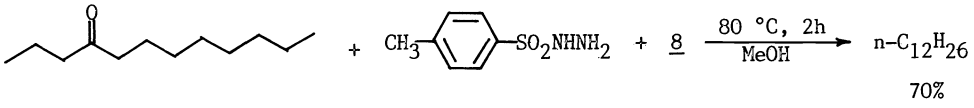

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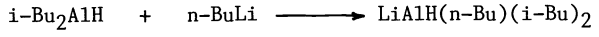
THE ATE COMPLEX FROM DIISOBUTYLALUMINUM HYDRIDE AND n-BUTYLLITHIUM

The reducing properties of alkali metal trialkylborohydrides have been intensively studied. However, there are only several reports in the literature on the use of lithium trialkylaluminum hydrides (ref. 22). Thus, the lack of systematic investigations of the reducing properties of these ate complexes prompted a detailed study of the reduction of a series of selected organic compounds containing various functional groups with the ate complex from Dibah and n-butyllithium in tetrahydrofuran-hexane and/or toluene-hexane (eq. 14) (ref. 8).

The simple primary alkyl bromide, 1-bromododecane, was reduced with the reagent (9) in tetrahydrofuran-hexane within 10 min at room temperature, whereas it was inert to the reagent at -78°C. The secondary alkyl bromide was reduced much more slowly than the primary alkyl bromide and the tertiary alkyl bromde was essentially inert to the reagent but trace amounts of elimination products were detected. Furthermore, the reagent rapidly reduced simple benzylic and allylic halides. The reactivity of organic halides toward the reagent makes possible selective reduction of primary bromides in the presence of secondary bromides (eq. 15). Of special synthetic significance is the stoichiometric requirement of the reagent (9) in the reduction of organic halides. Essentially complete utilization of the hydride of the reagent is in marked contrast with the results obtained from the reaction of organic halides with several hydride reducing agents (ref. 23). It has been reported that the reaction of alkyl halides with equimolar amounts of lithium triethylborohydride proceeds rapidly up to 50%, with further reaction being sluggish probably due to the formation of lithium triethylborohydride-triethylborane complex and 2 equiv of the reagent are required for the complete reduction. However, we expected that the bulkiness of lithium tri-sec-butylborohydirde (10) might prevent the formation of such complex. Indeed, it was found that the reduction of the primary alkyl bromide with a stoichiometric amount of lithium tri-sec-butylborohydride (10) proceeded to completion. In general, the efficiency and applicability of lithium tri-sec-butylborohydride were very similar to those of the reagent (9) (ref. 24).



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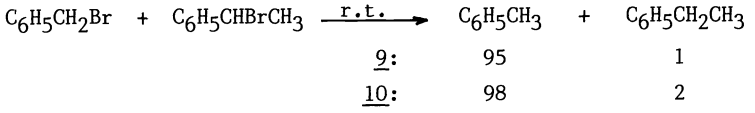

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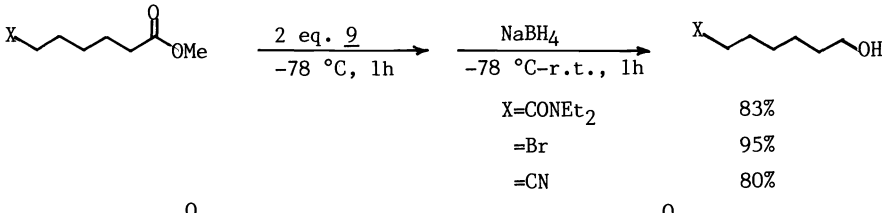

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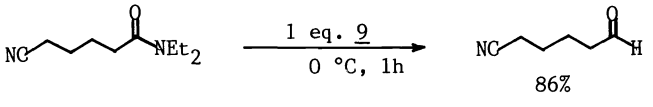

(17)

Esters and lactones were completely reduced to alcohols at room temperature, whereas they were reduced to a mixture of alcohols and aldehdyes at -78°C even with an excess amount of the reagent (9). Partial reduction of esters and lactones to aldehydes and lactols was not achieved. The reagent reduced acid chlorides and acid anhydrides but did not reduce carboxylic acids, primary, and secondary amides. Tertiary amides were cleanly reduced to aldehydes with a stoichiometric amount of the reagent at room temperature or at 0°C, whereas they were inert to the reagent at -78°C, which permitted the selective reduction of other reducible functional groups in the presence of the tertiary amide group. Unlike facile reduction of nitriles with Dibah, nitriles were only slowly reduced to the corresponding aldehydes. Systematic investigations of the reagent (9) toward various functional groups suggest the possibility of many selective reductions. For instance, selective reduction of esters in the presence of a tertiary amide, a bromide, and a nitrile can be achieved with the reagent (eq. 16). Furthermore, the reagent is capable of reducing selectively a tertiary amide in the presence of a nitrile (eq. 17).

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