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Partial Reduction of Nitriles to Aldehydes by Thexylbromoborane-Methyl Sulfide†

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A systematic study of the partial reduction of nitriles to the corresponding aldehydes with thexylbromoborane-methyl sulfide (ThxBHBr·SMe_2) under practical conditions has been carried out. The yields of aldehydes are good in the aliphatic series. However, the yields of aromatic series vary with substituents and ring itself.

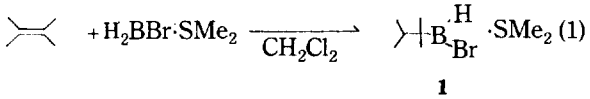
The conversion of carboxylic acid derivatives, such as acid chlorides[1], esters[2], amides[3], and nitriles[4], to the corresponding aldehydes is a very important synthetic route. Among them, the partial reduction of nitriles to aldehydes by reducing agents is one of the widely-used methods for such transformations. Diisobutylaluminum hydride[5] and lithium triethoxyaluminohydride[6] are considered as the major metal hydride reducing agent for this purpose. Very recently, Yoon and his coworkers reported that diethyldihydroaluminate achieves the partial reduction of aliphatic nitriles to aldehydes in the presence of diethylaluminum 2,6-di-*t*-butylphenoxide as a Lewis acid in high yields[7].

In the course of a systematic study of the reducing characteristics of thexylbromoborane-methyl sulfide[8], we have found that this reagent possesses the ability to reduce nitriles to aldehydes efficiently, even though this reagent appeared to be a mild reducing agent.

Therefore, we decided to study systematically such reduction in the hope of establishing a practical means.

Results and Discussion

The reagent, thexylbromoborane-methyl sulfide (1), is readily prepared by hydroborating 2,3-dimethyl-2-butene with monobromoborane-methyl sulfide in methylene chloride (eq 1). Monobromoborane-methyl sulfide is easily prepared by treating borane-methyl sulfide with a half equiv of bromine in carbon disulfide.



$$+ H_2BBr\cdot SMe_2 \xrightarrow{CH_2Cl_2} \text{Thx}(H)B(Br)\cdot SMe_2 \quad (1)$$

1

Thx = thexyl = 1,1,2-trimethylpropyl

Thexylbromoborane-methyl sulfide is a much milder and hence more selective reducing agent than thexylchloroborane-methyl sulfide[9]. Thus, the reagent tolerates many organic functionalities, *viz.*, esters, acid chlorides, epoxides, halides and nitro compounds. Besides, the most interesting feature of this reagent is its reluctance to hydroborate double bonds even at room temperature. The chloro-derivative readily hydroborates double bonds. However, the reagent attacks the triple bond of both aliphatic and aromatic nitriles readily and the aldehyde intermediate thus formed are relatively inert to the second attack of reagent. This suggested the possibility of achieving a synthesis of aldehydes from nitriles, even in the presence of other readily reducible groups.

† Dedicated to Professor Nung Min Yoon on the occasion of his 60th birthday.

Table 1. Reaction of Caprylonitrile with Thexylbromoborane-Methyl Sulfide under Various Conditions

Run	Reagent/Compd	Solvent	Reaction time (h)	Reaction temp (°C)	Yield(%)[a]
1	1	CH_2Cl_2	0.5	25	81
2	1.1	CH_2Cl_2	0.5	25	90
3	1.2	CH_2Cl_2	0.5	25	87
4	1.1	CH_2Cl_2	6.0	0	92
5	1.1	$CH_2Cl_2+CS_2$[b]	0.5	25	88
6	1.1	$CH_2Cl_2+CS_2$[b]	6.0	0	95[c]
7	1.5	$CH_2Cl_2+CS_2$[b]	6.0	0	84

[a] Analyzed by 2,4-dinitrophenylhydrazine. [b] 40 Volume % of CS_2 added. [c] Optimum condition.

Table 2. Reaction of Benzonitrile with Thexylbromoborane-Methyl Sulfide under Various Conditions

Run	Reagent/Compd	Solvent	Reaction time (h)	Reaction temp (°C)	Yield(%)[a]
1	1	CH_2Cl_2	6.0	25	65
2	1.1	CH_2Cl_2	24.0	25	60
3	1.2	CH_2Cl_2	24.0	25	60
4	1.1	$CH_2Cl_2+CS_2$[b]	24.0	25	71
5	1.5	$CH_2Cl_2+CS_2$[b]	24.0	25	72[c]

[a] Analyzed by 2,4-dinitrophenylhydrazine. [b] 40 Volume % of CS_2 added. [c] Optimum condition adopted for these reactions.

Reaction Conditions. In order to find out the optimum condition, various reaction conditions were examined systematically using caprylonitrile as a representative for aliphatics and benzonitrile as a representative for aromatics. The results are summarized in Table 1 and 2.

As shown in Table 1, the effect of reaction temperature was not significant for aliphatic series, however the results at 0°C were better than those at 25°C, even though the reaction requires 6 h for completion. The solvent effect did not show any significant difference. However, the addition of *ca.* 40 volume % of carbon disulfide resulted in the enhanced yield of aldehyde.

The effect of the ratio of reagent to compound was also examined. Considerable difference in results was noted. Therefore, it was concluded that the addition of 10% excess reagent to 1 equiv of compound in methylene chloride and carbon disulfide (40 volume %) at 0°C, followed by reduction for 6 h, is optimum for the reduction of aliphatic nitriles to aldehydes.

In the case of aromatic nitriles, as summarized in Table 2, the reaction was quite slow, hence required more drastic condition (24 h at room temperature). It was also observed that the addition of carbon disulfide (40 volume %) increases at least 10% in the yield of aldehyde. However, the effect of the ratio of reagent to compound was not significant, even with the use of 50% excess reagent. Therefore, it was concluded that the addition of 10% excess reagent to 1 equiv of compound in methylene chloride and carbon disulfide (40 volume %) at 25°C, followed by reduction for 24 h, is optimum for the reduction of aromatic nitriles to aldehydes.

Scope of the Reaction. The above optimum reaction conditions were applied to other representative nitriles and the results analyzed by 2,4-dinitrophenylhydrazine are

Table 3. Reaction of Aliphatic Nitriles with Thexylbromoborane-Methyl Sulfide at 0°C[a]

Nitrile	Yield of aldehyde analyzed by 2,4-dinitrophenylhydrazine(%)
Butyro-	83
Caprylo-	95 (85)[b]
Decane-	84
Isobutyro-	72
	78[c]
	69[d]
Isovalero-	81
	65[d]
Trimethylaceto-	60[e]
	60[f]
Cyclopropanecarbo-	60
Phenylaceto-	42
	9[d]
Diphenylaceto-	62
	65[g]
	54[h]
	49[d]
Adipo-	15[i]
Sebaco-	75

[a] The standard conditions (reagent: compound = 1.1:1; for 6 h at 0°C) was adopted, except otherwise indicated. [b] Isolated yield by sodium bisulfite adduct method. [c] Reacted for 19 h at 25°C. [d] Ratio of reagent to compound was 2:1. [e] Reacted for 72 h at 25°C. [f] Reacted for 19 h under reflux. [g] Reacted for 12 h. [h] Ratio of reagent to compound was 1.5:1. [i] Apparently decomposed in a strong acidic medium.

Table 4. Reaction of Aromatic Nitriles with Thexylbromoborane-Methyl Sulfide at Room Temperature[a]

Nitrile	Yield of aldehyde analyzed by 2,4-dinitrophenylhydrazine(%)
Benzo-	71 (60)[b]
	72[c]
Phthalo-	dec.
o-Tolu-	75
m-Tolu-	80
p-Tolu-	70
p-Nitrobenzo-	22
	20[d]
3-Cyanopyridine	4
	29[d]
	20[e]
4-Cyanopyridine	3
	52[d]
	48[e]
p-Carbohydroxybenzo-	91[e,f] (82)[b]

[a] The standard conditions (reagent: compound = 1.1:1; for 24 h at 25°C) was adopted, except otherwise indicated. [b] Isolated yield by sodium bisulfite adduct method. [c] Ratio of reagent to compound was 1.5:1. [d] Ratio of reagent to compound was 2:1. [e] Ratio of reagent to compound was 3:1. [f] Reacted for 9 h, terephthalaldehyde formed.

summarized in Table 3 and 4.

The reagent, ThxBHBr·SMe$_2$, reduces aliphatic nitriles, as shown in Table 3, in high yields. Especially, in the case of compounds with a straight alkyl chain, such as butyro-, caprylo- and decanenitrile, the reaction goes well in yields of 83-95%. However, the reaction of alkyl-substituted aliphatic nitriles, such as isobutyro- and trimethylacetonitrile, are much sluggish. The reaction requires a prolonged reaction time even at room temperature and the yields are somewhat lower (60-80%). Phenyl-substituted acetonitriles provide the aldehydes in yields of 42-65%. The reagent also reduces dinitriles to dialdehydes in high yields.

The results from aromatic nitriles are quite variable (Table 4), showing a significant influence of substituents and ring itself upon the yield. Thus, the yields for the unsubstituted aromatic nitrile (*i.e.*, benzonitrile) and those substituted with methyl group (*i.e.*, *o*-, *m*- and *p*-tolunitrile) are around 70-80%. However, the yields for nitrobenzonitrile and pyridinonitriles are quite low. The result form *p*-carbohydroxybenzonitrile is quite interesting. The reduction product is terephthalaldehyde in yield of 91% realized from the reaction with using 3 equiv of reagent. This result is well coincided with the fact that the reagent reduces carboxylic acids to aldehydes directly.[10]

The classical sodium bisulfite adduct procedure for the isolation of aldehyde products, adopted for the reduction of carboxylic acids with thexylchloroborane and thexylbromoborane, appeared also to be broadly applicable to this case. Thus, the isolated yields using this procedure are quite reasonable (*i.e.*, 85% for caprylonitrile, 60% for benzonitrile, and 82% for *p*-carbohydroxybenzonitrile).

Conclusion

It appears from this systematic study that thexylbromoborane-methyl sulfide provides another useful synthetic route from nitriles to the corresponding aldehyde. In view of its simplicity and selectivity to organic functional groups, this useful reagent should find valuable application for organic synthesis.

Experimental

All glasswares required for the experiments were dried thoroughly in a drying oven, assembled hot, and cooled under a stream of nitrogen just prior to use. All reactions were carried out under a static pressure of nitrogen in flasks fitted with septum-covered sidearms with use of standard techniques for handling air-sensitive materials.[11] All chemicals used were commercial products of the highest purity. Methylene chloride, carbon disulfide, and pentane were stirred for one day under nitrogen over P_2O_5 and then distilled. Tetrahydrofuran and methyl sulfide were dried over 4A molecular sieve and distilled from sodium-benzophenone ketyl prior to use. 2,3-Dimethyl-2-butene synthesized from pinacolone was distilled over lithium aluminum hydride and stored under nitrogen. ^{11}B NMR spectra were recorded on a Bruker FT-80 spectrometer, and the chemical shifts are reported relative to BF_3·OEt_2 with low field assigned as positive.

Preparation of Monobromoborane-Methyl Sulfide (BH_2Br·SMe_2) in Methylene Chloride.[12] To an oven-dried, 1-*l* flask equipped with a sidearm, and dry ice-acetone condenser with a stop cock leading to a mercury bubbler was added 150 m*l* (1.5 mole) borane-methyl sulfide (BMS) and 375 m*l* of carbon disulfide. Then to this 38.4 m*l* of bromine (0.75 mole) dissolved in 749 m*l* of carbon disulfide was added using a long double-ended needle dropwise with vigorous stirring. After the complete evolution of hydrogen, carbon disulfide was removed by simple distillation and finally monobromoborane-methyl sulfide was collected by distillation under the reduced pressure. The yield was almost quantitative.

Preparation of Thexylbromoborane-Methyl Sulfide (ThxBHBr·SMe_2) in Methylene Chloride. Monobromoborane-methyl sulfide (1.5 mole) in 66 m*l* of methylene chloride and 15 m*l* of methyl sulfide was placed in an oven-dried, 500-m*l* flask fitted with a sidearm and a bent-adaptor which was connected to a mercury bubbler. The flask was immersed in an ice-water bath and to this was added 196 m*l* of precooled 2,3-dimethyl-2-butene (1.65 mole) dropwise over a period of 1 h *via* a double -ended needle. The reaction mixture was stirred for an additional 2 h at 0°C, followed by stirring overnight at room temperature. The resulting thexylbromoborane-methyl sulfide (ThxBHBr·SMe_2) solution in methylene chloride was found to be 3.34 M and ^{11}B NMR spectrum showed a clean doublet centered at $\delta = 5.16$ ppm ($J_{B\text{-}H} = 123$ Hz).

Reduction of Nitriles. The reduction of caprylonitrile is described as a representative utilized in the quantitative analysis with 2,4-dinitrophenylhydrazine. To an oven-dried, 50-m*l* flask with a sidearm and a bent-adaptor connected to a mercury bubbler was added 3 mmole of caprylonitrile and 2 m*l* of carbon disulfide. The flask was immersed in an ice-water bath and to this was added dropwise 3.3 mmole of precooled ThxBHBr·SMe_2 (10% excess) *via* a hypodermic syringe. The reaction mixture was stirred for 6 h at 0°C and then all volatile materials were evaporated out under the reduced pressure. The residue was subjected to analysis with 2,4-dinitrophenylhydrazine,[13] showing a yield 95%.

Isolation of Aldehyde Products.[14] The procedure for isolation of capryloaldehyde using the sodium bisulfite adduct formation and formaldehyde regeneration method is representative. The reaction mixture of caprylonitrile (50 mmole) following the reduction for 6 h at room temperature (*vide ante*) was transferred using a double-ended needle to the flask containing 50 m*l* of cold water in an ice-water bath and hydrolyzed with vigorous stirring for 2 h at room temperature. The mixture was then saturated with sodium chloride. The separated organic layer was neutralized with a small quantity of sodium bicarbonate. And then the organic layer was poured into 75 m*l* of a saturated aqueous sodium bisulfite solution and 100 m*l* of THF was added. The mixture was stirred for 1 h. At this time, the crystalline bisulfite adduct of capryloaldehyde was apparent. The solution was cooled in an ice-water bath to insure complete crystallization of the adduct. The adduct was then collected by filtration and washed with 3×25 m*l* of pentane and dried. The solid adduct was placed in 50 m*l* of a saturated aqueous magnesium sulfate solution and then 50 m*l* of pentane and 8 m*l* of a 37% formaldehyde solution were added. The mixture was stirred for 1 h. The pentane layer was separated and dried with anhydrous magnesium sulfate. All volatile materials were evaporated and distillation of the crude product gave 85% of pure capryloaldehyde: b.p. 80-82°C (50 mm), $n^{20}_D = 1.4257$.

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Reaction of Di-*s*-butoxyborane in Tetrahydrofuran with Selected Organic Compounds Containing Representative Functional Groups. Catalytic Effect of Tetraalkoxyborate on the Reaction of Dialkoxyborane †

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The approximate rate and stoichiometry of the reaction of excess di-*s*-butoxyborane with selected organic compounds containing representative functional groups under standardized conditions (tetrahydrofuran, 25°C) was examined in order to define the characteristics of the reagent for selective reductions. And the catalytic effect of lithium tetra-*s*-butoxyborate on the reaction of di-*s*-butoxyborane was also studied in order to increase the utility of this reducing system. Di-*s*-butoxyborane reacts only with simple aldehydes. However the addition of 2.5 mole % of lithium tetra-*s*-butoxyborate shows the tremendous rate enhancement of reaction for aldehydes, ketones, anhydrides, acid chlorides, lactones, and epoxides. This catalytic effect is assumed to *in situ* formation of lithium trialkoxyborohydride.

The alkylboranes[1-3], as substituted boranes, exhibit their own unique reducing characteristics. This uniqueness and hence selectivity on the reduction of organic functionalities is of dependence upon the alkyl-substituents. In the same sense, the reducing properties of dialkoxyboranes should be varied with their alkoxy-substituents.

† Dedicated to Professor Nung Min Yoon on the occasion of his 60th birthday.