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Studies of Reduction with Dimethoxyborane–Transition Metal Salt Systems. I. Reduction of Nitriles, Aldehydes and Ketones with Dimethoxyborane–Transition Metal Salt Systems

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The reduction of a variety of functional groups with new dimethoxyborane–transition metal salt systems was investigated. The dimethoxyborane–cobaltous chloride system reduced nitriles and aldehydes under mild conditions in good yields, and the dimethoxyborane–nickelous chloride system similarly reduced nitriles, aldehydes, olefin and ketones. The other functional groups tested were unaffected by these systems.

Keywords reduction; nitrile; aldehyde; ketone; dimethoxyborane; transition metal salt; dimethoxyborane–cobaltous chloride system; dimethoxyborane–nickelous chloride system

Dimethoxyborane, prepared easily from diborane and methanol, reduces aldehydes and ketones,[1] and hydroborates olefins.[2] It was reported that the diborane–methanol system selectively reduced imines, while other functional groups, such as aldehyde, ketone, olefin and nitrile, were unaffected, and the actual reductant in this system was dimethoxyborane.[3] It was also reported that diborane–transition metal salt systems reduced nitrile as well as nitro and heterocyclic compounds to give the corresponding primary and secondary amines, though the yields of primary amines were unsatisfactory.[4] As a continuation of those studies, we investigated new dimethoxyborane–transition metal salt systems in order to improve the yield of primary amines in the reduction of nitriles. The present paper also deals with the reduction of olefin, aldehyde and ketone functional groups with this system.

Previously, it was reported that nitrile was not reduced with dimethoxyborane alone.[3] However, the dimethoxyborane–nickelous chloride ($NiCl_2$) or –cobaltous chloride ($CoCl_2$) system reduced nitriles (**1** and **2**) in methanol at room temperature to give the corresponding primary amines (**3** and **4**) and secondary amines (**5** and **6**) as shown in Table I. Similarly, as shown in Table II, nitrile derivatives (**7**—**12**) were reduced with this system.

Since the yields of primary amines increased with increasing amount of transition metal salt and lowering of the addition temperature (Table I), as shown in Table III, similar reactions using 1—5 eq of $CoCl_2$ at $-10\,^{\circ}C$—$-20\,^{\circ}C$ afforded the primary amines in good yields.

Furthermore, aldehydes were reduced under similar conditions to the corresponding alcohols, as shown in Table IV. However, the compounds bearing an electron-donating group at the *ortho* or *para* position exhibited poor reactivity. In particular, *o*-methylbenzaldehyde (**15**) and *p*-methoxybenzaldehyde (**17**) were inert to this system even if the addition temperature was raised to room temperature. The similar reaction of 3-phenylpropionaldehyde (**22**) afforded bis(3-phenylpropyl)ether in good yield.

Furthermore, olefin, ketone, carboxylic acid, ester and amide compounds were examined under similar conditions. As shown in Table V, the dimethoxyborane–$NiCl_2$ system reduced olefin and ketones. However, these functional groups except for that of cyclohexanone, which has high reactivity among ketones, were unaffected by the dimethoxyborane–$CoCl_2$ system, and carboxylic acid, ester and

Table I. Reduction of Benzonitrile (**1**) and Benzyl Cyanide (**2**) with the $BH(OCH_3)_2$–$CoCl_2$ or –$NiCl_2$ System at Room Temperature

Compd. No.	$BH(OCH_3)_2$ (eq)	$CoCl_2$ (eq)	$NiCl_2$ (eq)	Add. time (min)	Product (No.) yield (%) *prim*-Amine		*sec*-Amine	
1	8		1/2	50	**3**	Trace	**5**	76.8
1	8	1/4		30	**3**	28.9	**5**	46.4
1	16	1		50	**3**	35.3	**5**	37.4
1	16	1		50[a]	**3**	52.0	**5**	28.2
2	16	1		30	**4**	40.8	**6**	49.6

[a] Reaction temperature was 0 °C.

Table II. Reduction of Nitrile Derivatives (**7**—**12**) with the $BH(OCH_3)_2$–$CoCl_2$ or –$NiCl_2$ System at Room Temperature

R–CN R (No.)	$BH(OCH_3)_2$ (eq)	$CoCl_2$ (eq)	$NiCl_2$ (eq)	Add. time (min)	Product yield (%) *prim*-Amine	*sec*-Amine
o-$CH_3C_6H_4$ (**7**)	16	1		30	50.5	42.1
p-ClC_6H_4 (**8**)	16	1		30	27.0	52.0
p-$CH_3OC_6H_4CH_2$ (**9**)	12		1	30	80.0	Trace
p-$ClC_6H_4CH_2$ (**10**)	8		1/2	30	76.0	Trace
p-$H_2NC_6H_4CH_2$ (**11**)	16	1		30	97.7	
1-Naphthyl (**12**)	12	1		30	72.9	Trace

Table III. Reduction of Nitriles with the $BH(OCH_3)_2$–$CoCl_2$ System at -10 to $-20\,^{\circ}C$

R–CN R (No.)	$BH(OCH_3)_2$ (eq)	$CoCl_2$ (eq)	Add. temp. (°C)	Add. time (min)	Product yield (%) *prim*-Amine	*sec*-Amine
C_6H_5 (**1**)	16	5	−10	30	75.9	16.5
C_6H_5 (**1**)	12	1	−20	30	78.6	6.3
C_6H_5 (**1**)	16	5	−20	30	Trace	
o-$CH_3C_6H_4$ (**7**)	16	3	−10	30	80.2	3.6
o-$CH_3C_6H_4$ (**7**)	16	1	−20	30	89.9	7.3
p-ClC_6H_4 (**8**)	16	3	−10	30	71.1	9.4
p-$CH_3C_6H_4$ (**13**)	16	5	−10	30	75.6	10.2
$C_6H_5CH_2$ (**2**)	16	3	−10	30	73.5	5.7
$C_6H_5CH_2$ (**2**)	16	1	−20	30	93.0	6.2
p-$CH_3OC_6H_4CH_2$ (**9**)	16	1	−20	30	73.6	4.9
p-$ClC_6H_4CH_2$ (**10**)	16	5	−10	30	85.6	2.9

amide were not reduced by either system. Carboxylic acids tested were esterified; in particular, octanoic acid gave methyl octanoate under these mild conditions in good yield.

In order to compare the reducing ability of various transition metal salts, we examined the reduction of benzyl cyanide (**2**) with several dimethoxyborane–transition metal salt systems. As shown in Table VI, ferric chloride ($FeCl_3$) and cupric chloride ($CuCl_2$) did not exhibit reducing activity.

In the reduction with the dimethoxyborane–$CoCl_2$ system in methanol at -10°C, nitrile and aldehyde were reduced in good yields, whereas the nitro group (Table IV), olefin, ketone, carboxylic acid, ester and amide (Table V) were unaffected. In particular, it is noteworthy that only aldehyde among the carbonyl compounds, except for cyclohexanone, was reduced with this system. On the other hand, the selectivity of the dimethoxyborane–$NiCl_2$ system was inferior to that of the dimethoxyborane–$CoCl_2$ system, since olefin and ketone were reduced with the dimethoxyborane–$NiCl_2$ system (Table V).

Reports of reduction using dimethoxyborane–transition metal salt have apparently not been published previously. Heizman and Ganem[5] reported merely that *tert*-butylamine–borane reduced nitriles in refluxing methanol in the presence of cobalt boride and suggested that the reductant might be surface-generated BH_3.

As described above, the dimethoxyborane–$CoCl_2$ system can provide a useful and simple method for the selective reduction of nitrile and aldehyde functional groups in synthetic chemistry.

Table IV. Reduction of Aldehydes (**14**—**22**) with the $BH(OCH_3)_2$–$CoCl_2$ System

$$\text{R–CHO} \xrightarrow{\text{BH(OCH}_3)_2,\ \text{CoCl}_2} \underset{\text{A}}{\text{R–CH}_2\text{OH}}(+\underset{\text{B}}{(\text{R–CH}_2)_2\text{O}})$$

R–CHO R (No.)	$BH(OCH_3)_2$ (eq)	$CoCl_2$ (eq)	Add. temp. (°C)	Add. time (min)	Yield (%) A	Yield (%) B
C_6H_5 (**14**)	16	3	-10	30	93.7	
o-$CH_3C_6H_4$ (**15**)	16	3	-10	30	Recovery[a]	
p-$CH_3C_6H_4$ (**16**)	16	3	-10	30	53.5	
p-$CH_3OC_6H_4$ (**17**)	16	3	-10	30	Recovery[a]	
o-ClC_6H_4 (**18**)	16	3	-10	30	98.9	
p-ClC_6H_4 (**19**)	16	3	-10	30	88.2	
o-$O_2NC_6H_4$ (**20**)	16	3	-10	30	95.6	
p-$O_2NC_6H_4$ (**21**)	16	3	-10	30	80.4	
$C_6H_5CH_2CH_2$ (**22**)	16	3	-10	30		99.6

a) Reduction also did not proceed at room temperature.

Experimental

Commercially available $NiCl_2 \cdot 6H_2O$, $CoCl_2 \cdot 6H_2O$, $FeCl_3 \cdot 7H_2O$, $CuCl_2 \cdot 2H_2O$, $NaBH_4$ and boron trifluoride etherate were used throughout this work. Melting points were determined on a Yanagimoto micromelting point apparatus (model MP-S3), and are uncorrected. Infrared (IR) spectra were recorded on a JASCO Uvidec-505 spectrometer. Gas chromatography (GC) was done on a Nihon Denshi JGC-20K (SE-30), and chromatography columns of alumina were prepared with Aluminiumoxide 90 (70—230 mesh ASTM, Merck). Nuclear magnetic resonance (NMR) spectra were recorded on a Hitachi R20-A spectrometer.

Reduction of Nitriles The procedure for the reduction of **2** with the dimethoxyborane–$CoCl_2$ system will be described in detail as a typical example. Compound **2** (0.5 g, 4.27 mmol) and $CoCl_2 \cdot 6H_2O$ (1.02 g, 4.27 mmol) were dissolved in methanol (30 ml). Then, diborane[6] (B_2H_6) (68.3 mmol) was passed into the solution for 30 min at -20 °C with stirring and the mixture was allowed to stand for 10 min. After removal of the solvent, 10% hydrochloric acid (20 ml) was added at 0 °C, and the precipitate was collected and washed with ether. The precipitate was recrystallized from ethanol to give diphenethylamine (**6**) hydrochloride as colorless needles, mp 268—269.5 °C (lit.[7] mp 271 °C). This precipitate was

Table V. Reduction of a Variety of Functional Groups with $BH(OCH_3)_2$–Transition Metal Salt Systems

Compound (No.)	$BH(OCH_3)_2$ (eq)	$CoCl_2$ (eq)	$NiCl_2$ (eq)	Add. temp. (°C)	Add. time (min)	Product	Yield (%)
$CH_3(CH_2)_9CH=CH_2$ (**23**)	16		5	-10	30	$CH_3(CH_2)_{10}CH_3$	74.1
$CH_3(CH_2)_9CH=CH_2$ (**23**)	16	5		-10	30	Recovery[a]	
$C_6H_5COCH_3$ (**24**)	16		5	-10	30	$C_6H_5CH(OH)CH_3$	80.4
$C_6H_5COCH_3$ (**24**)	16	5		-10	30	Recovery[a]	
$CH_3(CH_2)_6COCH_3$	16	5		-10	30	Recovery[a]	
Cyclohexanone (**25**)	16		5	-10	30	$C_6H_{11}OH$	83.7
Cyclohexanone (**25**)	16	5		-10	30	$C_6H_{11}OH$	64.0
C_6H_5COOH	16		5	-10	30	$C_6H_5COOCH_3$	15.4
C_6H_5COOH	16	3		-10	30	$C_6H_5COOCH_3$	3.2
$CH_3(CH_2)_6COOH$	16	3		-10	30	$CH_3(CH_2)_6COOCH_3$	74.7
$C_6H_5CH_2COOC_2H_5$	16		5	-10	30	Recovery[a]	
$C_6H_5CH_2COOC_2H_5$	16	5		-10	30	Recovery[a]	
$C_6H_5CH_2NHCOCH_3$	16		5	-10	30	Recovery[a]	
$C_6H_5CH_2NHCOCH_3$	16	5		-10	30	Recovery[a]	

a) Reduction also did not proceed at room temperature.

Table VI. Comparison of the Reducing Ability of $BH(OCH_3)_2$–Transition Metal Salt Systems

Compound	$BH(OCH_3)_2$ (eq)	TMS[a]	TMS[a] (eq)	Add. temp. (°C)	Product yield (%) $C_6H_5CH_2CH_2NH_2$	Product yield (%) $(C_6H_5CH_2CH_2)_2NH$
$C_6H_5CH_2CN$	16	$CoCl_2$	3	-10	73.5	5.7
$C_6H_5CH_2CN$	16	$NiCl_2$	5	-10	76.3	6.6
$C_6H_5CH_2CN$	16	$FeCl_3$	5	-10	—	—
$C_6H_5CH_2CN$	16	$CuCl_2$	5	-10	—	—

a) TMS = transition metal salt.

suspended in water, and the suspension was basified by the addition of 10% sodium hydroxide, followed by extraction with ether. The extract was dried over anhydrous magnesium sulfate. After removal of the ether, the residue was distilled under reduced pressure to give 30 mg (6.2%) of **6** as a colorless oil, bp 172—173 °C (8 mmHg) (lit.[8]) bp 170—175 °C (8 mmHg)). The picrate was obtained as yellow needles (from ethanol), mp 151—152 °C (lit.[9]) mp 151—152 °C). The acidic aqueous layer treated above was basified by the addition of concentrated ammonium hydroxide, followed by extraction with ether. The extract was dried over anhydrous magnesium sulfate. After the ether was evaporated off, the residue was distilled to give 481 mg (93.0%) of phenethylamine (**4**), bp 196—198 °C. Products **4** and **6** were identical with authentic samples, based on comparisons of IR, ultraviolet (UV) and NMR spectra, and gas chromatographic behavior.

Compounds **1**—**13** were reduced similarly; the reaction conditions and results are listed in Tables I, II and III. These products were identical with corresponding authentic samples based on comparisons of IR, VU and NMR spectra, and gas chromatographic behavior.

Reduction of Aldehydes Benzaldehyde (**14**) (0.5 g, 4.72 mmol) and $CoCl_2 \cdot 6H_2O$ (3.35 g, 14.16 mmol) were dissolved in methanol (30 ml). Then B_2H_6[6]) (37.76 mmol) was passed into the solution for 30 min with stirring at −10 °C and the reaction mixture was allowed to stand for 10 min at room temperature. After removal of the solvent, water (20 ml) was added, followed by extraction with ether. The extract was dried over anhydrous magnesium sulfate. After removal of the ether, the residue was distilled to give 477 mg (93.7%) of benzyl alcohol as a colorless oil, bp 94—97 °C (12 mmHg) (lit.[10]) bp 94 °C (10 mmHg)). This product was identical with an authentic sample based on comparisons of IR, UV and NMR spectra.

Compounds **15**—**22** were reduced under similar conditions, followed by treatment as described above. The reaction conditions and results are listed in Table IV. The products were identical with the corresponding authentic samples based on comparisons of IR, UV and NMR spectra, and gas chromatographic behavior.

Reduction of Compounds 23—25 Compounds **23**—**25** were reduced with dimethoxyborane–transition metal salt systems under the conditions shown in Table V followed by treatment in the manner described above. The products were identical with the corresponding authentic samples, based on comparisons of IR, UV and NMR spectra and gas chromatographic bahavior.

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