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A New Reduction of Some Carboxylic Esters with Sodium Borohydride and Zinc Chloride in the Presence of a Tertiary Amine

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In the presence of a tertiary amine, sodium borohydride ($NaBH_4$) combined with zinc chloride ($ZnCl_2$) showed powerful reducing properties and carboxylic esters were smoothly reduced to their corresponding alcohols which were not obtained by reduction with $NaBH_4$ and $ZnCl_2$ alone. Tetrahydrofuran (THF) was an efficient solvent, and the effective molar ratio of the reducing agents, $NaBH_4 : ZnCl_2$: tertiary amine, was 2 : 1 : 1. In particular, aminobenzoates such as anthranilic esters, were reduced to aminobenzyl alcohols with high yields without the addition of a tertiary amine. Further, it was also found that this combination reduced nitro, cyano, and amido groups to their corresponding amino groups.

It is known that $NaBH_4$ does not usually reduce carboxylic esters. However, several reports have suggested the possibility of $NaBH_4$ reduction of ester groups. The esters were reported to be reduced by using a large excess (20 equiv) of $NaBH_4$ in methanol,[1] and esters having complex-forming neighboring functional groups, such as oxo[2] or hydroxy esters[3] can be reduced. Soai et al. reported an efficient reducing system with $NaBH_4$-*t*-butyl alcohol–methanol for esters,[4] and Kitsuki and Fujikura reported the reduction with $NaBH_4$-2-(2-ethoxyethoxy)ethanol–xylene.[5]

On the other hand, Kollonitsch et al. reported briefly that carboxylic esters are reduced with $NaBH_4$ in the presence of a metal halide such as lithium, magnesium or calcium halide.[6] Further, Brown et al. reported the utility of aluminium chloride ($AlCl_3$) as a metal halide to be used in combination with $NaBH_4$.[7]

In this paper, a new reduction system, a combination of $NaBH_4$ and $ZnCl_2$ in the presence of a tertiary amine, by which carboxylic esters can be reduced smoothly to their corresponding alcohols with high yields, is reported.

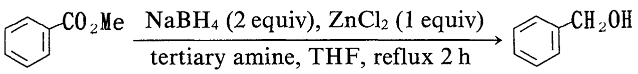
Results and Discussion

Methyl benzoate was reduced successfully with 2.0 equiv of $NaBH_4$ and 1.0 equiv of $ZnCl_2$ in the presence of 1.0 equiv of *N,N*-dimethylaniline in THF under reflux conditions to produce an 82% isolated yield of benzyl alcohol as shown in Scheme 1. Triethylamine was similarly proved to be a very effective tertiary amine. Only 8% yield of benzyl alcohol was obtained in the absence of the tertiary amine. *N,N*-Dimethylaniline was preferable as a tertiary amine to triethylamine, because the latter formed a complex with BH_3 in the reaction mixture, which led to difficulty in separation and purification of the product.

Reduction of benzoates with bromo, alkylthio, nitro, and hydroxy moieties was carried out under the same conditions. The results are shown in Table 1.

A bromo or benzylthio group on the benzene ring had little or no influence on the reduction of the ester function. Reduction of methyl 4-nitrobenzoate gave 4-nitrobenzyl alcohol in a rather low yield probably owing to the competitive reduction of the nitro group. In the case of methyl 4-hydroxybenzoate, *p*-cresol was obtained in a 52% isolated yield possibly owing to further reduction of the 4-hydroxybenzyl alcohol initially produced. Similar reduction was reported by Brewster et al. in which 4-methoxybenzyl alcohol was reduced to 4-methylanisole with $LiAlH_4$–$AlCl_3$.[8]

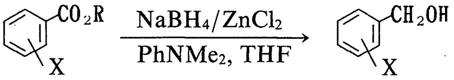
As shown in Table 2, various other esters could also be reduced to their corresponding alcohols with satisfactory isolated yields. However, the reduction of ethyl



		Yield
tertiary amine:	*N,N*-dimethylaniline	82%
	: triethylamine	80%
	: none	8%

Scheme 1.

Table 1. Reduction of Substituted Benzoate Derivatives[a)]

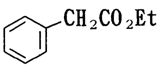
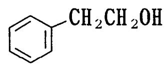
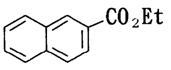
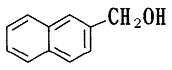
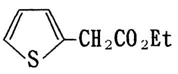
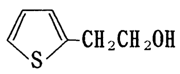
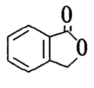
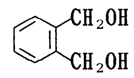
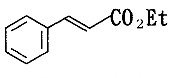
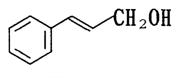


X	R	Yield/%
2-Br	Me	89
$2\text{-}SCH_2Ph$	Et	98
$4\text{-}NO_2$	Me	56
4-OH	Me	52[b)]

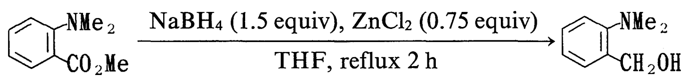
a) A mixture of a substituted benzoate (1.0 mmol), $NaBH_4$ (2.0 mmol), $ZnCl_2$ (1.0 mmol), and *N,N*-dimethylaniline (1.0 mmol) was refluxed in THF for 2 h and all products isolated gave satisfactory ^1H NMR spectra. b) *p*-Cresol was obtained.

Table 2. Reduction of Aromatic and Aliphatic Esters$^{a)}$

$$RCO_2R^1 \xrightarrow[\text{PhNMe}_2,\ \text{THF}]{\text{NaBH}_4/\text{ZnCl}_2} RCH_2OH$$

Ester	Alcohol	Yield/%
		85
		79
		82
$CH_3(CH_2)_{16}CO_2Me$	$CH_3(CH_2)_{16}CH_2OH$	99
		79
		46

a) A mixture of an ester (1.0 mmol), $NaBH_4$ (2.0 mmol), $ZnCl_2$ (1.0 mmol), and *N,N*-dimethylaniline (1.0 mmol) was refluxed in THF for 2 h, and all products isolated gave satisfactory ^{1}H NMR spectra.

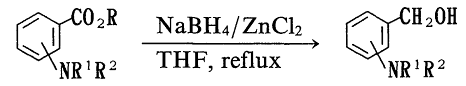


1　**2**

Yield 95%

Scheme 2.

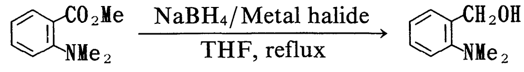
Table 3. Reduction of Aminobenzoate Derivatives$^{a)}$



NR^{1}R^2	R	Yield/%
2-NHMe	Me	81
2-NH_2	Me	79
2-$NEt_2$$^{b)}$	Et	96
3-NMe_2	Me	96

a) A mixture of an aminobenzoate (1.0 mmol), $NaBH_4$ (2.0 mmol), and $ZnCl_2$ (1.0 mmol) was refluxed in THF for 2 h and the structure of all products isolated was determined by ^{1}H NMR and elemental analyses (C, H, N±0.3). b) This compound was reduced with 1.5 mmol of $NaBH_4$ and 0.75 mmol of $ZnCl_2$.

Table 4. Reduction of **1** with $NaBH_4$ and Metal Halide$^{a)}$



1　**2**

Metal halide	mmol$^{b)}$	Yield$^{c)}$/%
$ZnCl_2$	0.75	95
LiCl	1.5	0
LiBr	1.5	0
$CaCl_2$	0.75	14
$MgCl_2$	0.75	0
$FeCl_2$	0.75	44
$ZnBr_2$	0.75	11
$BF_3{\cdot}OEt_2$	0.5	41
$SnCl_4$	0.5	10
$AlCl_3$	0.5	85$^{d)}$

a) A mixture of **1** (1.0 mmol), $NaBH_4$ (1.5 mmol), and an appropriate metal halide was refluxed in THF for 2 h. b) An equimolar amount of an additive required for metal borohydride was used, except for $SnCl_4$. c) Established by GC analysis with benzyl alcohol as an internal standard. d) The reduction was carried out at 25 °C for 24 h.

cinnamate gave a 46% yield of cinnamyl alcohol together with the double bond-reduced product.

Our reaction conditions were applied to reduction of a few esters with tertiary amino groups, and the reduction was expected to proceed smoothly in the absence of the tertiary amine. Thus, methyl *N,N*-dimethylanthranilate (**1**) could be reduced with 1.5 equiv of $NaBH_4$ and 0.75 equiv of $ZnCl_2$ without the addition of *N,N*-dimethylaniline to give 2-dimethylaminobenzyl alcohol (**2**) as shown in Scheme 2.

Furthermore, the reductions of other aminobenzoates with this reducing system were investigated. These results are summarized in Table 3.

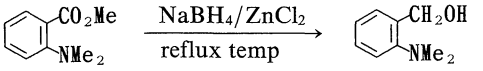
Dialkylamino benzoates were reduced to their corresponding benzyl alcohols with high yields, but the yields were somewhat low in the cases of *N*-unsubstituted or *N*-monoalkyl-substituted derivatives.

Various metal halides were investigated in place of $ZnCl_2$ in the reduction of methyl *N,N*-dimethylanthranilate (**1**). The yield of 2-dimethylaminobenzyl alcohol (**2**) was determined by gas chromatographic (GC) analysis. The results are summarized in Table 4. Lithium and magnesium halide did not enhance the reducing ability of $NaBH_4$, in spite of Kollonitsch's report mentioned above. However, $AlCl_3$ showed a good effect as reported by Brown et al.,[7] and the reduction proceeded at room temperature but was accompanied by the formation of some decomposition products possibly owing to the strong Lewis acidity of $AlCl_3$.

Solvent effects were investigated in the reduction of methyl *N,N*-dimethylanthranilate (**1**) with $NaBH_4$ and $ZnCl_2$ under refluxing for 2 h. As shown in Table 5, no reduction product was obtained in ethers such as diethyl ether, diisopropyl ether (IPE), and dioxane, but the reduction product was obtained in a low yield in dimethyl ether of diethylene glycol (diglyme). The reduction in ethanol produced only a small amount of ester-exchanged product without the reduction product. THF was the most suitable solvent for this reduction possibly owing to the solubility of the reagents.

The mechanism of the present reduction might be

Table 5. Reduction of **1** with $NaBH_4$ and $ZnCl_2$ in Various Solvents[a)]

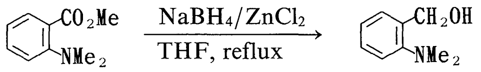


1 **2**

Solvent	Yield[b)]/%
THF	95
Ether	0
IPE	0
Dioxane	0
Diglyme[c)]	22
EtOH	0[d)]

a) A mixture of **1** (1.0 mmol), $NaBH_4$ (1.5 mmol), and $ZnCl_2$ (0.75 mmol) was refluxed in each solvent for 2 h. b) Established by GC analysis with benzyl alcohol as an internal standard. c) The reaction was carried out at 25 °C for 24 h. d) A small amount of ester-exchanged product was detected.

Table 6. Reduction with Varying Molar Ratios of $NaBH_4$ and $ZnCl_2$[a)]



1 **2**

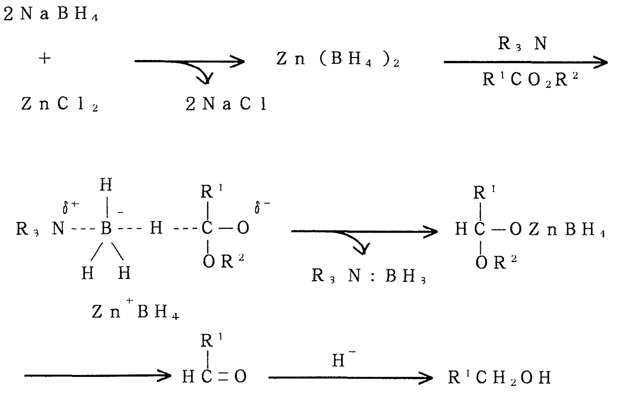
$ZnCl_2$	Yield[b)]/%	
mmol	1 h	2 h
0	0	0
0.5	49	63
0.75	100	100
1.5	93	92

a) 1.5 mmol of $NaBH_4$ to 1.0 mmol of **1** was used. b) Established by GC analysis with benzyl alcohol as an internal standard.

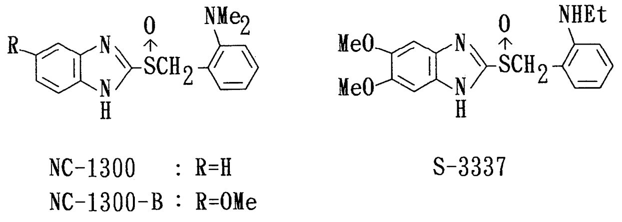
explained by the initial formation of $Zn(BH_4)_2$ followed by the reduction of esters with $Zn(BH_4)_2$ which is activated by a tertiary amine. In order to clarify this, the reduction was studied by varying the molar ratio of $NaBH_4$ and $ZnCl_2$ as shown in Table 6.

When the molar ratio of $NaBH_4$ and $ZnCl_2$ was 2 : 1, the corresponding 2-dimethylaminobenzyl alcohol (**2**) was produced quantitatively after 1 h. Use of less $ZnCl_2$ served to slow down the rate of the reaction, while use of more $ZnCl_2$ gave a small amount of decomposition product after 1 h owing to the Lewis acidity of $ZnCl_2$, and no appreciable increase of reduction product was observed even after a prolonged reaction time. These results also suggested the formation of $Zn(BH_4)_2$. The formation of $Zn(BH_4)_2$ from $NaBH_4$ and $ZnCl_2$ has been reported by Gensler et al.[9)]

Furthermore, the optimum molar ratio of $NaBH_4$ to **1** was proved to be 1.5 : 1, while the reduction with an equimolar amount of $NaBH_4$ to **1** afforded ca. an 80% yield of **2** after 4 h. The curve of reaction yield showed that the reaction would be completed only after a prolonged reaction time. These results revealed that only one hydride on $NaBH_4$ was effective for the reduction of an ester group to an aldehyde. A possible mechanism is shown in Scheme 3.



Scheme 3.



Scheme 4.

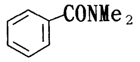
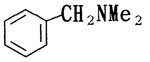
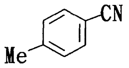
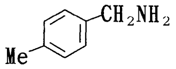
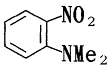
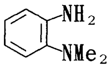
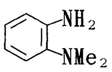
This reduction technique using $NaBH_4$–$ZnCl_2$–tertiary amine seems very useful because of the possibility of industrial applications in place of reductions with $LiAlH_4$ which is flammable and expensive. For example, the reduction of anthranilates is necessary for producing 2-aminobenzyl alcohols which are key intermediates of new H^+/K^+-ATPase inhibitors[10)] as shown in Scheme 4. The reduction of anthranilate has been performed successfully only by using $LiAlH_4$.[11)]

Further, the applicability of this reduction system to the reduction of other functional groups, such as amide, nitro, and cyano groups, was studied. The results are shown in Table 7. *N,N*-Dimethylbenzamide and 4-methylbenzonitrile were reduced to the corresponding benzylamine in good yields. However, the yield of the product in the reduction of 2-dimethylaminonitrobenzene without a tertiary amine was relatively low; the addition of *N,N*-dimethylaniline increased the yield. It seemed that the electron-withdrawing nitro group in the molecule decreased the basicity of the tertiary amino group.

Experimental

Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL JNM-FX90Q NMR spectrometer with

Table 7. Reduction of Other Functional Groups[a)]

Starting material	Amine	Product	Yield/%
	PhNMe$_2$		84
	PhNMe$_2$		79
	NONE		40
	PhNMe$_2$		85

a) A mixture of a substrate (1.0 mmol), NaBH$_4$ (2.0 mmol), and ZnCl$_2$ (1.0 mmol) in the presence or absence of *N,N*-dimethylaniline (1.0 mmol) was refluxed in THF for 2 h, and the structure of all products isolated was determined by ^{1}H NMR and elemental analysis (C, H, N±0.3).

tetramethylsilane as the internal standard. GC analyses were performed on a 1.0 m column of 1% SE-30 on a JEOL JGC-20K gas chromatograph, operating at 30—200 °C. Elemental analyses (C,H,N) were performed on a Heraus C,H,N-Rapid instrument.

Materials. Sodium borohydride and metal halides (lithium chloride, lithium bromide, calcium chloride, magnesium chloride, iron(III) chloride, zinc chloride, zinc bromide, boron trifluoride–diethylether (1/1), tin(IV) chloride, and aluminum chloride) were commercially available. Tetrahydrofuran was purified through aluminum oxide. Commercial diglyme was distilled over calcium hydride and then redistilled under reduced pressure from a small quantity of lithium aluminum hydride. Other etheric solvents, such as diethyl ether, diisopropyl ether, and dioxane, were purified by standard methods followed by a distillation from lithium aluminum hydride. Commercial ethanol (95%) was utilized without further purification. *N,N*-Dimethylaniline, triethylamine, methyl benzoate, methyl 4-nitrobenzoate, methyl 4-hydroxybenzoate, ethyl phenylacetate, ethyl 2-thiopheneacetate, methyl stearate, phthalide, ethyl cinnamate, methyl *N,N*-dimethylanthranilate (**1**), methyl *N*-methylanthranilate, methyl anthranilate, *N,N*-dimethylbenzamide, and 4-methybenzonitrile were commercially available. Ethyl *N,N*-diethylanthranilate was prepared by ethylation of ethyl anthranilate with diethyl sulfate. Ethyl 2-benzylthiobenzoate was prepared by esterification of 2-mercaptobenzoic acid followed by alkylation with benzyl bromide. Methyl 3-dimethylaminobenzoate, ethyl 2-naphthalenecarboxylate, and methyl 2-bromobenzoate were prepared by esterification of the corresponding carboxylic acids. *N,N*-Dimethyl-2-nitroaniline was prepared by the standard method.[12)]

Reduction of Methyl Benzoate. A mixture of methyl benzoate (13.6 g, 100 mmol), NaBH$_4$ (7.60 g, 200 mmol), ZnCl$_2$ (13.6 g, 100 mmol), and *N,N*-dimethylaniline (12.1 g, 100 mmol) was refluxed with stirring in THF (200 ml) for 2 h. The reaction mixture was cooled with ice-cold water, and 10% NH$_4$Cl solution and chloroform were added. The organic layer was separated, washed with water and saturated NaCl solution, and dried over anhydrous Na$_2$SO$_4$. The solvent was evaporated and distilled to give 8.86 g (82% yield) of benzyl alcohol as a colorless oil. Reduction of substituted benzoates and other aromatic and aliphatic esters was carried out by a similar procedure. The results are summarized in Tables 1 and 2.

Reduction of Methyl *N,N*-Dimethylanthranilate (1). A mixture of **1** (1.79 g, 10.0 mmol), NaBH$_4$ (570 mg, 15.0 mmol), and ZnCl$_2$ (1.02 g, 7.5 mmol) was refluxed in THF (50 ml) for 2 h. The reaction mixture was cooled with ice-cold water, and 10% NH$_4$Cl solution and chloroform were added. The organic layer was separated, washed with water and saturated NaCl solution, and dried over Na$_2$SO$_4$. The solvent was evaporated and the residue was purified on a silica-gel column (chloroform) to produce 1.43 g (95% yield) of 2-dimethylaminobenzyl alcohol (**2**) as a colorless oil. ^{1}H NMR (CDCl$_3$) δ=2.68 (s, 6H), 4.78 (s, 2H), 6.9—7.3 (m, 4H). Other aminobenzoate derivatives were reduced by a procedure similar to that described for **1**. The results are summarized in Table 3.

General Procedure for the Study on the Effect of Metal Halides. A mixture of **1** (1.0 mmol), NaBH$_4$ (1.5 mmol), and an appropriate metal halide (0.5—1.5 mmol) was refluxed with stirring in THF (5 ml) for 2 h. The yield of 2-dimethylaminobenzyl alcohol (**2**) was determined by GC analysis with benzyl alcohol as an internal standard. The results are summarized in Table 4.

General Procedure for the Study of Solvent Effects. A mixture of **1** (1.0 mmol), NaBH$_4$ (1.5 mmol), and ZnCl$_2$ (0.75 mmol) in a solvent (5 ml) was refluxed with stirring for 2 h. The yield of **2** was determined by GC analysis with benzyl alcohol as an internal standard. The results are summarized in Table 5.

General Procedure for the Study of the Effect of the Molar Ratio of NaBH$_4$ and ZnCl$_2$. A mixture of **1** (1.0 mmol), NaBH$_4$ (1.5 mmol), and ZnCl$_2$ (0, 0.5, 0.75, 1.5 mmol) in THF (5 ml) was refluxed with stirring for 2 h. The yield of **2** was determined by GC analysis with benzyl alcohol as an internal standard. The results are shown in Table 6.

General Procedure for the Reduction of Other Functional Groups. A mixture of an amide, nitro or cyano compound (1.0 mmol), NaBH$_4$ (2.0 mmol), and ZnCl$_2$ (1.0 mmol) in the presence or absence of *N,N*-dimethylaniline (1.0 mmol) in THF (5 ml) was refluxed with stirring for 2 h. The reaction was quenched with 20% NH$_4$Cl solution and the reaction mixture was extracted with CHCl$_3$. The organic layer was washed with saturated NaCl, dried over anhydrous Na$_2$SO$_4$, and the solvent was evaporated in vacuo. The residue was purified on a silica-gel column (ether–hexane) to give the corresponding reduced compound. The yields are summarized in Table 7.

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