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Practical Procedure for the Chemoselective Reduction of Esters by Sodium Borohydride. Effect of the Slow Addition of Methanol[1]

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The effect of solvents on the reduction of esters was examined with readily available sodium borohydride which is known to be incapable of reducing such functional groups. In mixed solvents of *t*-butyl alcohol–methanol or tetrahydrofuran–methanol, various carboxylic esters and lactones were found to be reduced by sodium borohydride to the corresponding alcohols or diols in high yields. Slow addition of methanol to the refluxing mixture of ester and sodium borohydride in *t*-butyl alcohol or tetrahydrofuran was essential to achieve effective reduction. On the other hand, each individual solvent, methanol or *t*-butyl alcohol, was not effective for the reduction. The procedure provided a practical method for the functional group selective reduction of esters in the presence of chloro, cyano, carboxylato, carbamoyl, carboxy or nitro groups, which can not usually be performed by lithium aluminium hydride.

We wish to report here a practical and selective reduction of esters and lactones with sodium borohydride ($NaBH_4$) in mixed solvent of *t*-butyl alcohol(*t*-BuOH)–methanol(MeOH), and in tetrahydrofuran(THF)–MeOH.

$NaBH_4$, since its discovery by Schlesinger, Brown and co-workers,[2] has enjoyed extensive use in the reduction of ketones and aldehydes. $NaBH_4$ is presently one of the most easily available among many complex metal hydrides, it is easier to manipulate than lithium aluminium hydride($LiAlH_4$) and lithium borohydride because of its lower sensitivity towards moisture.[3]

Though selective reduction of esters is an important method in organic synthesis,[4] $LiAlH_4$ can not usually be used for the purpose because of its excessive reducing power.[3] On the other hand, it is generally accepted that $NaBH_4$, a mild reducing agent, does not effectively reduce carboxylic esters.[5] If the reduction of esters with $NaBH_4$ is realized, the procedure may open the route to the reduction of esters with excellent functional group selectivities. Reduction of esters with $NaBH_4$ in ethanol(EtOH)[6] or MeOH[7] result in the formation of alcohols only in low yields. High reaction temperature (300 °C),[8] use of polyethylene glycol (PEG 400) of high boiling point[9] or metal salt additive[10] is required for the reduction of esters with $NaBH_4$.

We recently reported that $NaBH_4$ in mixed solvent of THF and a protic solvent shows much higher stereoselectivity than in each individual solvent in asymmetric reduction of chiral α-keto amides.[11] We describe in this paper the details of the study on solvents and the scope and limitations of the selective reduction of esters with $NaBH_4$ in mixed solvents.

Results and Discussion

In order to study the effect of mixed solvents (solvent A and solvent B) on the reduction of esters by $NaBH_4$, methyl benzoate (**1**) was chosen as a model compound. Solvent B (0.8 ml) was added slowly (1 h) to the mixture of **1** (1 mmol) and $NaBH_4$ (2.1—2.6 mmol) in solvent A (4 ml) at various temperatures. The reactions were quenched by the addition of water or dil. HCl,[12] and the yields of the resulting benzyl alcohol (**2**) were determined by GLC. For comparison, reductions in single solvents, MeOH or *t*-BuOH, were also run. The results are summarized in Table 1.

$$\underset{(1)}{PhCO_2Me} \xrightarrow[\text{solvent A and solvent B}]{NaBH_4} \underset{(2)}{PhCH_2OH}$$

The following conclusions and comments may be drawn from the data in Table 1: (1) Reduction in a single solvent of MeOH afforded **2** in only 11% yield (Entry 1) and vigorous evolution of gas (probably hydrogen) was observed when $NaBH_4$ and MeOH were mixed. This low yield of the alcohol was in accord with the previously reported result of the reduction of ester with $NaBH_4$ in MeOH.[7] (2) The yield of **2** was only 6% when reaction was run in a single solvent of *t*-BuOH (Entry 2). *t*-BuOH seemed to be almost inert to $NaBH_4$.[10c] (3) A dramatic result was obtained when MeOH was added to the refluxing mixture of $NaBH_4$ and **1** in *t*-BuOH. The yield of **2** increased 88% (Entry 3).[13] (4) Furthermore, combination of THF and MeOH was found to be more effective. The yield of **2** reached 97% (Entry 6). (5) Reduction at refluxing

Table 1. Effect of solvent and temperature on the reduction of methyl benzoate (**1**) by sodium borohydride[a]

$$\underset{(1)}{PhCO_2Me} \xrightarrow[\text{solvent A and solvent B}]{NaBH_4} \underset{(2)}{FhCH_2OH}$$

Entry	Solvent[b] A–B	Temp. /°C	Time /h	Yield of **2**, %[c]
1	MeOH	reflux	2.0	11
2	*t*-BuOH	reflux	2.0	6
3	*t*-BuOH–MeOH	reflux	2.0	88
4	*t*-BuOH–MeOH	r.t.	2.0	3
5	*t*-BuOH–*i*-PrOH	reflux	2.5	20
6	THF–MeOH	reflux	2.0	97
7	*i*-PrOH–MeOH	reflux	2.0	38
8	Et_2O–MeOH	reflux	2.0	38
9	Benzene–MeOH	reflux	3.0	11
10	Diglyme–MeOH	50	4.5	60

a) Molar ratio $NaBH_4$: ester = 2.5 : 1.0. b) Volumetric ratio of solvent A : B = 5 : 1. c) Yields determined by G.L.C.

temperature (88%, Entry 3) afforded a higher yield of **2** than that at room temperature (3%, Entry 4). (6) As co-solvent, MeOH (88%, Entry 3) was more effective than 2-propanol (20%, Entry 5). (7) $NaBH_4$ is known to be soluble in diglyme.[3c] Reduction at 50 °C gave a moderate yield (60%) of **2** (Entry 10). However there remains a possibility of a higher yield in the reduction run at a higher temperature. (8) $NaBH_4$ was not soluble in the mixed solvent of benzene and MeOH and the yield of **2** was low (Entry 9). (9) Low yield (38%) of **2** in ether and MeOH (Entry 8) was probably due to the lower reaction temperature than that of THF–MeOH (Entry 6). (10) *t*-BuOH was more effective than 2-propanol (Entries 3 and 7).

As described, the addition of MeOH to the refluxing mixture of methyl benzoate (**1**) and $NaBH_4$ in *t*-BuOH or THF was very effective for the conversion of **1** to benzyl alcohol (**2**). It is also of interest that the mixed solvent of *t*-BuOH and MeOH (Table 1, Entry 3) was much more effective than the separate individual solvents, *t*-BuOH (Entry 2) or MeOH (Entry 1).

From the standpoint of synthesis, the present method has the following advantages over the procedure using PEG 400[9] (1) High yields using lesser amount of $NaBH_4$. (2) Shorter reaction time. (3) An easier working-up procedure because of the use of solvents of lower boiling points (MeOH, *t*-BuOH, THF). (4) Easier control of the rate of evolution of the hydrogen formed by the reaction between MeOH and $NaBH_4$. In the case of PEG 400, evolution of hydrogen, formed by reaction between PEG and $NaBH_4$, is reported during the warming of the reaction mixture.[9] On the other hand, the present procedure includes the slow addition of MeOH to the refluxing mixture of $NaBH_4$ and ester in THF or *t*-BuOH. Therefore, the rate of the evolution of gas by the reaction of MeOH and $NaBH_4$ is limited by the amount of MeOH added (reaction between *t*-BuOH and $NaBH_4$ is negligible,[10c] Table 1, Entry 2).

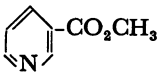
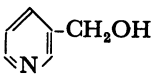
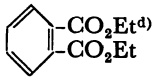
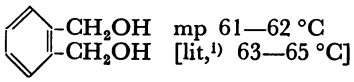
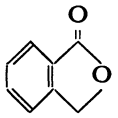
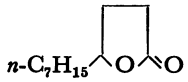
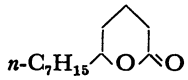
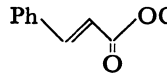
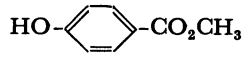
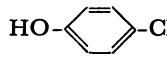
We then examined if the present procedure of the reduction of **1** is applicable to other esters and lactones. In a similar manner, reduction of various esters and lactones by $NaBH_4$ was performed either in mixed solvents of *t*-BuOH–MeOH or THF–MeOH. As clearly seen from the data summarized in Table 2, aliphatic, aromatic, heterocyclic mono- and diesters, in all cases, gave the corresponding alcohols in high yields. Diesters such as diethyl phthalate gave 1,2-benzenedimethanol in 91% yield and phthalide in 8% yield (Entry 14). Lactones afforded the corresponding diols in high yield, too (Entries 15 and 16). Even esters of sterically hindered carboxylic acids such as methyl 2-ethylbutanoate and methyl 2,2-dimethylpropanoate were reduced in high yields (Entries 3 and 4). The effect of the structure of the alcohol moiety of the esters was examined using various kinds of benzoates (Entries 5—12). Methl and ethyl benzoates were reduced in high yields (Entries 5, 6 and 7), and isopropyl benzoate afforded a moderate yield of **2** (Entries 8 and 9). However *t*-butyl benzoate was reduced only in low yield (Entries 10 and 11) Reduction of an α,β-unsaturated ester was accompanied by the reduction of the carbon–carbon double bond (Entry 17).[6] Methyl *p*-hydroxybenzoate was not reduced and was recovered unchange (Entry 18).[14]

The results of the preceding paragraphs suggested the possibility of a selective reduction of esters by the reducing system used. In fact, when compounds other than esters such as benzamide, *N,N*-dimethylbenzamide or 1-chlorodecane (**3**) were treated with $NaBH_4$ in refluxing *t*-BuOH–MeOH, no reduction products were obtained and all the substrates were recovered in 100%, 98%, and 93% yield respectively. In order to establish the synthetic utility of the reduction of esters by $NaBH_4$ in mixed solvents, we examined the competitive or selective reduction of esters in the presence of other groups.[15] The results are shown in Table 3.

A mixture of equimolar amounts of methyl benzoate (*1*) and 1-chlorodecane (**3**) was treated with $NaBH_4$ in refluxing *t*-BuOH–MeOH. **1** was reduced selectively to afford benzyl alcohol(2) in the yield of 82%, whereas 88% of **3** was recovered (Entry 1). Similarly, in the competitive reduction carried out in THF–MeOH, **2** was obtained in 88% yield and the recovery of **3** was 88% (Entry 2). Similarly, in the competitive reduction of esters in the presence of benzonitrile (Entries 3 and 4), sodium benzoate (Entry 5) benzamide (Entry 6) or benzoylglycine (Entry 9), esters were reduced selectively in moderate to high yields (49—97%). Whereas substrates other than esters were recovered in high yields (84—97%). Sodium benzoate was recovered as benzoic acid (85%, Entry 5). The ethoxycarbonyl group of ethyl *p*-nitrobenzoate was reduced selectively to afford *p*-nitrobenzyl alcohol in high yields (Entries 7 and 8). As described above, reduction by $NaBH_4$ in mixed solvents is useful for the selective reduction of esters in the presence of other functional groups such as chloro, cyano, carboxylato, carbamoyl, carboxy or nitro.

It is reported that hydroxylic solvents play an important role in the reduction of ketones with $NaBH_4$.[16] Hydroxylic solvents are incorporated in the mechanism of the reduction.[16] In inert solvents such as diglyme, reductions of ketones by $NaBH_4$ do not proceed to any appreciable extent.[17] Though it is not yet clear, we tentatively assume the following possibilities, (1) and/or (2), for the unusually high yields of the reduction of esters by the addition of MeOH to the refluxing mixture of $NaBH_4$ and esters in *t*-BuOH or THF. (1) MeOH as a protic solvent may play the same role as in the reductions of ketones by $NaBH_4$ in hydroxylic solvent.[16] (2) When MeOH reacts with $NaBH_4$, various alkoxyhydroborate(−1) are formed, *i.e.* $BH_3(OMe)^-$, $BH_2(OMe)_2^-$, $BH(OMe)_3^-$. These species or their aggregated form may show higher reducing power than $NaBH_4$, and may be capable of reducing esters.[18,22] Detailed discussion of the mechanistic aspects of the reduction of esters with $NaBH_4$ in mixed solvents must await further investigation. Low yields of the reduction of esters with $NaBH_4$ in single solvents of MeOH(Table 1, Entry 1) or EtOH[6] may be attributed to the high concentration of protic solvents. When a large amount of MeOH or EtOH exists, hydrides of $NaBH_4$ are rapidly consumed by the reaction with hydroxylic solvents especially at reflux temperatures. On the other hand, slow addition of MeOH to the mixture of $NaBH_4$ and ester in the present study may suppress this side reaction because the concentration of MeOH is much

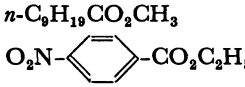
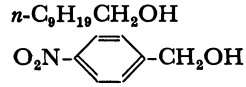
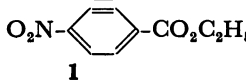
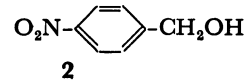
Table 2. Reduction of esters and lactones by $NaBH_4$[a] in mixed solvents of *t*-BuOH-MeOH or THF-MeOH

Entry	Ester or lactone	Mixed solvent[b]	Product	Yield/%[c]
1	$CH_3(CH_2)_8CO_2CH_3$	THF-MeOH	$CH_3(CH_2)_8CH_2OH$	90
2	$CH_3(CH_2)_{16}CO_2CH_3$	*t*-BuOH-MeOH	$CH_3(CH_2)_{16}CH_2OH$	79
3	$(C_2H_5)_2CHCO_2CH_3$	*t*-BuOH-MeOH	$(C_2H_5)_2CHCH_2OH$	84[e]
4	$(CH_3)_3CCO_2CH_3$	*t*-BuOH-MeOH	$(CH_3)_3CCH_2OH$	76[e]
5	$PhCO_2CH_3$ (**1**)	THF-MeOH	$PhCH_2OH$ (**2**)	97[e]
6	$PhCO_2CH_2CH_3$[d]	*t*-BuOH-MeOH	**2**	83[e]
7	$PhCO_2CH_2CH_3$[d]	THF-MeOH	**2**	83[e]
8	$PhCO_2i\text{-}Pr$[d]	*t*-BuOH-MeOH	**2**	60[e]
9	$PhCO_2i\text{-}Pr$[d]	THF-MeOH	**2**	63[e]
10	$PhCO_2t\text{-}Bu$[d]	*t*-BuOH-MeOH	**2**	17[e]
11	$PhCO_2t\text{-}Bu$[d]	THF-MeOH	**2**	24[e]
12	$PhCO_2CH_2Ph$[d]	*t*-BuOH-MeOH	**2**	98[e,f]
13		*t*-BuOH-MeOH		78
14		*t*-BuOH-MeOH	 mp 61—62 °C [lit,[i] 63—65 °C]	91
				8
15		*t*-BuOH-MeOH	$n\text{-}C_7H_{15}CH(OH)(CH_2)_2CH_2OH$	91
16		*t*-BuOH-MeOH	$n\text{-}C_7H_{15}CH(OH)(CH_2)_3CH_2OH$	89
17		THF-MeOH	$PhCH{=}CH\text{-}CH_2OH$	29[g]
18		*t*-BuOH-MeOH		0[h]

a) Molar ratio $NaBH_4$: ester = 2.5 : 1.0, unless otherwise noted. b) Refluxing temperature. c) Yields of isolated pure products unless otherwise noted. d) Molar ratio $NaBH_4$: ester = 5.0 : 1.0. e) Yields determined by GLC. f) Two moles of **2** were produced by the reduction of benzyl benzoate. g) Cinnamyl alcohol (29%), 3-phenylpropanol (50%) and methyl 3-phenylpropanoate (11%). Yields determined by NMR analysis. h) Recovery of the ester was 70%. i) Ref. 24.

Table 3. Selective or competitive reduction of esters in the presence of other groups (A) by $NaBH_4$ in mixed solvents[a]

$$\text{Ester} + \text{A} \xrightarrow[\text{t-BuOH-MeOH or THF-MeOH}]{NaBH_4} \text{Alcohol} + \text{A}$$

Entry	Ester	Compound of other group (A)	Solvent	Product yield/%[b]		Recovery A/%[c]
1	$PhCO_2CH_3$ (**1**)	$n\text{-}C_9H_{19}CH_2Cl$ (**3**)	*t*-BuOH-MeOH	$PhCH_2OH$ (**2**)	82	88
2	**1**	$n\text{-}C_9H_{19}CH_2Cl$ (**3**)	THF-MeOH	**2**	81	88
3	**1**	PhCN	*t*-BuOH-MeOH	**2**	61[d]	87[d]
4	**1**	PhCN	THF-MeOH	**2**	72[d]	84[d]
5	$n\text{-}C_9H_{19}CO_2CH_3$	$PhCO_2Na$	*t*-BuOH-MeOH	$n\text{-}C_9H_{19}CH_2OH$	74	85[e]
6	$n\text{-}C_9H_{19}CO_2CH_3$	$PhCONH_2$	*t*-BuOH-MeOH	$n\text{-}C_9H_{19}CH_2OH$	75	97
7			*t*-BuOH-MeOH		89	
8			THF-MeOH		88	
9	**1**	$PhCONHCH_2CO_2H$	*t*-BuOH-MeOH	**2**	49	87

a) Molar ratio (ester : A : $NaBH_4$ = 1.0 : 1.0 : 2.5), at refluxing temperature. b) Isolated yields unless otherwise noted. c) Isolated recovery. d) Determined by GLC. e) Recovered as benzoic acid after acidic treatment.

lower than that in single solvent of MeOH.

Conclusion

The addition of MeOH to a refluxing mixture of $NaBH_4$ and esters or lactones in *t*-BuOH or THF enabled the reduction of carboxylic esters or lactones to the corresponding alcohols or diols in high yields. The method provided synthetically useful selective reduction of esters in the presence of other reducible groups. Advantages of the method are the availability and easy manipulation of the reagents ($NaBH_4$, *t*-BuOH, THF, MeOH) and easy working-up because of the low boiling points of the solvents.

Experimental

Melting points were not corrected. IR spectra were recorded with a Hitachi 260-10 spectrophotometer. ^{1}H-NMR spectra (60 MHz) were recorded by using either a Varian EM-360A NMR spectrometer or a JEOL JNM- PMX-60 NMR spectrometer. GLC analyses were carried out with a Shimadzu Gas Chromatograph either model GC-4C or model GC-4A. All of the reaction were run under an atmosphere of argon.

Materials. 2-Propanol and benzene were stored over 4 Å molecular sieves. Methanol was stored over 3Å molecular sieves. *t*-Butyl alcohol was purchased from Kanto and was used without further purification. Tetrahydrofuran and diglyme were distilled from lithium aluminum hydride prior to use.

$NaBH_4$ (Nakarai) was used without further purification. Its activity (99%) was determined following a similar procedure described in the literature.[22] Most of the organic compounds utilized in this study were commercial products of high purity (Tokyo Kasei, Nakarai), but they were further purified by distillation when necessary. Methyl 2-ethylbutanoate was synthesized from the corresponding acid and MeOH using a catalytic amount of sulfuric acid according to the standard procedure: bp. 131—132 °C, lit,[23] bp. 135—137 °C (736 mm) .

Procedure for The Study of The Effect of Mixed Solvents and Temperature on The Reduction of Methyl Benzoate (1) by $NaBH_4$ (Table 1) Solvent B (0.8 ml) was added over a period of 1 h to the refluxing mixture of **1** (0.136 g, 1 mmol) and $NaBH_4$ (0.079—0.098 g, 2.1—2.6 mmol) in solvent A (4 ml). The reaction mixture was refluxed for an additional 1 h or more, and then 1—2 ml of diluted HCl or water was added. Most of the organic solvents of A and B were evaporated on a rotary evaporator. Naphthalene in ether was added to the residue. The yields of benzyl alcohol (**2**) were determined by GLC using naphthalene as internal standard (2 m glass column of 10% PEG 20M (1 M=1 mol dm^{-3}) on Chromosorb W AW, column temperature 140—170 °C, carrier gas He, TC detector).

General Procedure for The Reduction of Esters or Lactones by $NaBH_4$ in Mixed Solvents of t-BuOH-MeOH or THF-MeOH (Table 2). Methanol (0.8 ml) was added over a period of 1 h to the refluxing mixture of $NaBH_4$ (1 mmol) and ester or lactone (1 mmol) in *t*-BuOH (4 ml) or THF (4 ml). After the addition of MeOH, the reaction mixture was refluxed for an appropriate period. The reaction was quenched by the addition of diluted HCl or H_2O.

(1) The resulting alcohols were isolated according to the following procedure. Most of the organic solvents were evaporated on a rotary evaporator, and the residue was extracted with dichloromethane (6×5 ml). The combined extracts were dried over anhydrous sodium sulfate. After the evaporation of the solvent under reduced pressure, the residue was purified on preparative silica gel TLC. The NMR and IR spectra were identical with those of authentic samples.[24]

1,4-Undecanediol (Entry 15): NMR ($CDCl_3$) 0.6—1.8 (m, 19H), 3.3—3.75 (m, 3H), 4.0 (broad, 2H); IR (neat) 3320, 2950, 2870, 1470, 1070 cm^{-1}. Found: C, 70.12; H, 12.81%. Calcd for $C_{11}H_{24}O_2$: C, 70.16; H, 12.85%.

1,5-Dodecanediol (Entry 16): Mp 43.5—44.2 °C; NMR ($CDCl_3$) 0.6—1.9 (m, 21H), 3.0 (s, 2H), 3.4—3.8 (m, 3H); IR (KBr) 3280, 2920, 2850, 1460, 1380, 1138, 1108, 1065, 920 cm^{-1}. Found: C, 71.27; H, 12.88%. Calcd for $C_{12}H_{26}O_2$: C, 71.23; H, 12.95%.

(2) In the determination of the yields by gas chromatography, appropriate internal standards were added to the quenched reaction mixture and GLC analyses then carried out. The conditions of GLC analyses were as follows: for benzyl alcohol (**2**) (Entries 5—12), 2-m glass column of 10% PEG 20M on Chromosorb W AW, column temp. 145 °C, internal standard: naphthalene, TC detector; for 2-ethyl 1-butanol (Entry 3), capillary column SE-30, column temp. 45 °C, 2,2-dimethyl 1-propanol (internal standard), FI detector; for 2,2-dimethyl 1-propanol (Entry 4), capillary column SE-30, column temp. 45 °C, 2-ethyl 1-butanol (internal standard), FI detector.

Competitive Reduction of The Mixture of Methyl Benzoate (1) and 1-Chlorodecane or Benzonitrile (Table 3, Entry 1—4). Equimolar mixtures of methyl benzoate (**1**) (1 mmol) and 1-chlorodecane (1 mmol) or benzonitrile (1 mmol) were reduced with $NaBH_4$ in *t*-BuOH-MeOH or THF-MeOH according to the procedure described in the preceding paraph. Benzyl alcohol (**2**) (81—82%) and 1-chlorodecane (88%) (Entries 1 and 2) were purified on preparative silica gel TLC using dichloromethane as developing solvent. Yield of **2** (61—72%) and recoveries of benzonitrile (84—87%) (Entries 3 and 4) were determined by GLC analyses (2-m glass column of 10% PEG 20M on Chromosorb W AW, column temperature 140 °C, FI detector, with naphthalene as internal standard).

Competitive Reduction of The Mixture of Methyl Decanoate and Sodium Benzoate (Table 3, Entry 5). An equimolar mixture of methyl decanoate (1 mmol) and sodium benzoate (1 mmol) was reduced with $NaBH_4$ in *t*-BuOH-MeOH as described above. The reaction was quenched with water, and the solution made alkaline by adding 1M aq NaOH. The mixture was extracted with dichloromethane. The extracts were dried over anhydrous sodium sulfate, and evaporated on a rotary evaporator. Purification on silica gel TLC [developing solvent dichloromethane:ether (6:1)] gave 1-decanol in 74% yield. The 1-decanol synthesized was identical with an authentic sample in GLC analysis. Benzoic acid was recovered according to the following procedure. The water layer was acidified by diluted HCl, and extracted with dichloromethane and evaporated on a rotary evaporator. Purification on silica gel TLC [developing solvent dichloromethane:ether (6:1)] gave benzoic acid in 85% recovery.

Competitive Reduction of The Mixture of Methyl Decanoate and Benzamide (Table 3, Entry 6). An equimolar mixture of methyl decanoate and benzamide was reduced with $NaBH_4$ in t-BuOH-MeOH as described above. Purification on silica gel TLC [developing solvent CH_2Cl_2:MeOH (20:1)] afforded 1-decanol in 75% yield and benzamide in 97% recovery.

Reduction of Ethyl p-Nitrobenzoate (Table 3, Entries 7, 8). Ethyl *p*-nitrobenzoate was reduced with $NaBH_4$ in *t*-BuOH-MeOH or THF-MeOH. Silica gel TLC purification [developing solvent CH_2Cl_2:MeOH (10:1)] gave *p*-nitrobenzyl alcohol in 88—89% yield. mp 90—91 °C (lit,[22] mp 92—93 °C); ^{1}H NMR ($CDCl_3$) 2.15 (s, 1H, OH), 4.8 (s, 2H, CH_2), 7.4—8.3 (dd, 4H, aromatic protones); IR (KBr) 3540, 1610, 1518, 1345, 1065, 748 cm^{-1}.

Effect of The Molar Ratio of $NaBH_4$ and Methyl Benzoate (1) **1** was reduced in THF-MeOH using various amounts of $NaBH_4$ according to the procedure described in preceding paragraphs. Yields are those of the benzyl alcohol (**2**) isolated.

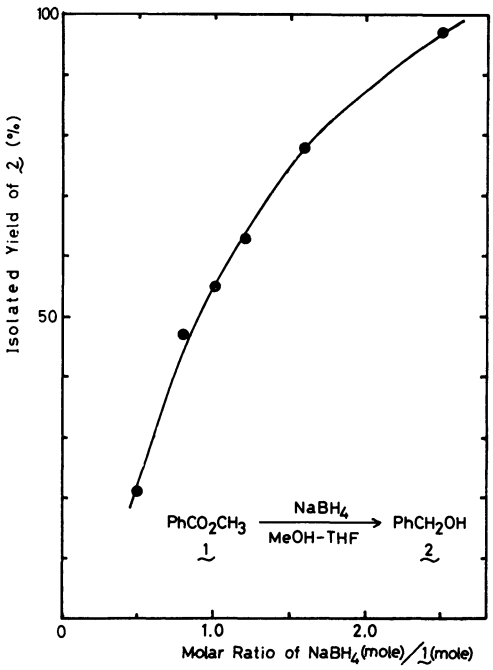


Fig. 1. Effect of Molar Ratio.

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12) No significant difference in the yield of benzyl alcohol (**2**) was observed between the methods of quenching. Yields of **2** by the addition of water or dil. HCl were 63% and 62% respectively in comparative reductions of **1**.

13) Slow addition of MeOH was more effective than rapid addition. When MeOH (12 mmol) was added to the mixture of ($NaBH_4$ 2.5 mmol) and **1** (1 mmol) before heating, the yield of **2** dropped to 64%. Interestingly, hydride of the reagent remained even after reflux. Despite this molar ratio of $NaBH_4$ and MeOH (1.0:4.8), evolution of gas (hydrogen) was observed when the reaction was quenched with dil. HCl.

14) Methyl *p*-hydroxybenzoate is known to resist reduction. See ref. 9.

15) When different groups are attached to the same molecule, the selectivity may be changed by neighbouring group participation. On the other hand, even pairs of groups of the same type have been differentiated by virtue of their steric environment in the molecule which has a rather rigid skeleton. Therefore we assume that competitive reduction is on a suitable scale for the functional group selectivity of the reaction. a) F. C. Huang, L. F. H. Lee, R. S. D. Mittal, P. R. Ravikumar, J. A. Chan, C. J. Sih, E. Caspi, and C. R. Eck, *J. Am. Chem. Soc.*, **97**, 4144 (1975); b) P. A. Bell and M. B. Gravestock, *Can. J. Chem.*, **47**, 2099 (1969).

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18) Sodium hydrotrimethoxyborate [$NaBH(OCH_3)_3$] is known to undergo rapid disproportionation into $NaBH_4$ and sodium tetramethoxyborate in THF.[19]

$$4\,NaBH(OCH_3)_3 \xrightarrow[THF]{} NaBH_4 + 3\,NaB(OCH_3)_4$$

Though reduction of esters with $NaBH(OCH_3)_3$ is reported, $NaBH(OCH_3)_3$ reduces the esters only slowly in ether at reflux or in dibutyl ether at high temperatures(100—140 °C)[20] with the exception of the reduction in dimethoxyethane at reflux.[15b]

To clarify whether all the reducing species are formed *in situ* $NaBH(OCH_3)_3$ in the reduction of esters by $NaBH_4$ in THF-MeOH, effect of the molar ratio of $NaBH_4$ and ethyl benzoate (**1**) was studied in the mixed solvent of THF and MeOH. Results are shown in Fig. 1. The yield of benzyl alcohol (**2**) increased with increase of $NaBH_4$. It become clear that $NaBH(OCH_3)_3$ is not the only reducing species, at least when the molar ratio of $NaBH_4$ to ester (**1**) is between 0.8—1.2. The reason is as follows: $NaBH(OCH_3)_3$ has only one active hydride[21] and one ester needs two active hydrides to be reduced to the corresponding alcohol. If $NaBH(OCH_3)_3$ were the only reducing species and if the reduction proceeded quantitatively, the yield of **2** could not exceed 50% when equimolar amounts of $NaBH_4$ and **1** were used. However, the actual isolated yield of **2** was 55% using equimolar amounts of $NaBH_4$ in mixed solvent of THF and MeOH.

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21) It is not meant in this text that "active hydride" is the actual species. The term is used only for the purpose of easy counting.

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