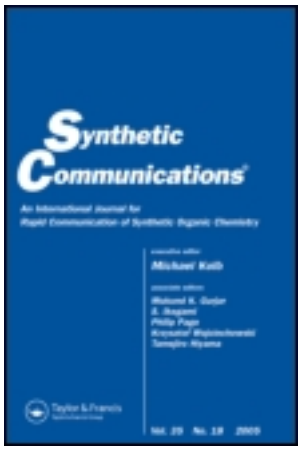


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Reductions of Carboxylic Acids and Esters with $NaBH_4$ in Diglyme at 162°C

Hua-Jie Zhu [a] & Charles U. Pittman Jr. [a]

[a] University/Industry Chemical Research Center, Department of Chemistry, Mississippi State University, Mississippi State, Mississippi, USA

Version of record first published: 17 Aug 2006

To cite this article: Hua-Jie Zhu & Charles U. Pittman Jr. (2003): Reductions of Carboxylic Acids and Esters with $NaBH_4$ in Diglyme at 162°C, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 33:10, 1733-1750

To link to this article: http://dx.doi.org/10.1081/SCC-120018935


MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

SYNTHETIC COMMUNICATIONS®
Vol. 33, No. 10, pp. 1733–1750, 2003

Reductions of Carboxylic Acids and Esters with $NaBH_4$ in Diglyme at 162°C

Hua-Jie Zhu and Charles U. Pittman Jr.*

University/Industry Chemical Research Center,
Department of Chemistry, Mississippi State University,
Mississippi State, Mississippi, USA

ABSTRACT

Aromatic esters, including the extremely sterically hindered ester: *t*-amyl 2-chlorobenzoate, are readily reduced to the corresponding benzyl alcohols in high yield with $NaBH_4$ in refluxing diglyme (162°C). In sharp contrast, aliphatic esters usually gave only low yields of alcohols. Instead, diglyme fragmentation products are formed which undergo transesterification reactions, producing complex product mixtures including products such as $RCOOCH_2CH_2OCH_3$. The mechanism of this process involves sodium borohydride-induced S_N2 cleavage of diglyme (hydride attack) at high temperatures. However, when the extremely electron rich, 3,4,5-trimethoxybenzoic acid is

*Correspondence: Charles U. Pittman Jr., University/Industry Chemical Research Center, Department of Chemistry, Box 9573 Mississippi State University, Mississippi State, MS 39762, USA; Fax: (662) 328-7611; E-mail: cpittman@ra.msstate.edu.

DOI: 10.1081/SCC-120018935 0039-7911 (Print); 1532-2432 (Online)

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

treated with $NaBH_4$/diglyme at 162°C (with or without an equivalent of LiCl), no 3,4,5-trimethyoxybenzyl alcohol is formed. The electron rich and hindered ester, *t*-amyl-3,4,5-trimethoxybenzoate, also does not reduce under these conditions (with or without LiCl). However, both methyl and isopropyl 3,4,5-trimethoxybenzoate esters were converted into 3,4,5-trimethyoxybenzyl alcohol in good yields in $NaBH_4$/diglyme/LiCl at 162°C. These reductions did not occur unless LiCl was present, illustrating the electron releasing effect of the three methoxy functions which reduce the carbonyl group's reactivity.

Key Words: Sodium borohydride; Reductions; Diglyme; Transesterification; Carboxylic acids; Esters.

INTRODUCTION

The reduction of aliphatic esters with sodium borohydride in protic solvents is extremely slow and therefore not practiced for industrial processes. In aprotic solvents, such as dichloromethane, the reduction of ethyl laurate with tetrabutylammonium borohydride is only 25% complete after four days at 25°C.[1] However, if an electron withdrawing atom or functional group is adjacent to the carbonyl group, the reduction can be carried out. This has been demonstrated when the electron withdrawing group is an epoxy,[2] chloro,[3,4] or cyano function.[5] Some saturated acids and esters can be reduced to alcohols by combining $NaBH_4$ and $AlCl_3$ at room temperature.[6,7] Unsaturated acids or esters formed complex compounds under these conditions.[6,7] Esters have been reduced by $NaBH_4$ when catalyzed by LiCl (or LiI) in THF.[8–10] Other metallic ions, such as $TiCl_4$[11] and $CaCl_2$[12–14] were used to enhance the reduction efficiency of $NaBH_4$ in various reductions. Reductions of aromatic carboxylic acids and aromatic esters with $NaBH_4$ in diglyme at 162°C have been actively investigated in our laboratory under a variety of conditions, both with and without LiCl present.[15] Ethyl benzoate was readily reduced to benzyl alcohol at high temperature in diglyme. Aromatic amides and nitriles were also reduced under these conditions.[15,16] High temperature borohydride reductions also can dechlorinate aromatic chloro compounds such as 4-chlorobiphenol and PCBs.[17] Aliphatic esters and carboxylic acids have not been studied under comparable conditions.

As part of a general effort to extend the utility of $NaBH_4$, we have examined its use at high temperature in order to determine if $NaBH_4$ will be able to effect reductions which currently require $LiAlH_4$, $LiEt_3BH$, and other more expensive and more difficult to handle hydride reducing reagents. $NaBH_4$ is thermally stable. Nevertheless, very few studies of its reductions at high temperature have appeared. It has usually been used in hydroxylic solvents. When heated in water or alcohols, BH_4^- reacts to produce hydrogen, limiting its application temperature. $NaBH_4$ has low solubility in most solvents which has limited its application.

Herein, we report the $NaBH_4$ reductions of both aromatic and aliphatic carboxylic acids in diglyme at 162°C. Furthermore, representative alkyl esters of both aromatic and aliphatic carboxylic acids were treated with $NaBH_4$ at 162°C. Cinnamic acids and aliphatic esters of cinnamic acids also reacted under these conditions but gave poor yields of cinnamyl alcohol.

EXPERIMENTAL

General

All chemicals were purchased from Aldrich Company except for diglyme which was a gift from Ferro Corporation. ^{1}H NMR spectra were obtained on a General Electric QE-300 instrument. A Varian 3300 GC was used (DB-5, 30 m). GC/MS were obtained on a Varian Saturn 2000 instrument. Melting points were uncorrected. Many of the esters were synthesized. ^{1}H NMR spectra and/or mass spectrometry data are summarized together after the example syntheses.

Typical Procedure for the Syntheses of Esters

Methyl 2-chlorobenzoate (3): NEt_3 (450 μL, 3.2 mmol) was added to a methanol solution of 2-chlorobenzoyl chloride (525 mg, 3.0 mmol) at room temperature. After 10 h most of the methanol was evaporated under reduced pressure (30–40 mmHg). The residue was washed with water and then extracted with ethyl acetate. The ethyl acetate extract was dried over sodium sulfate, filtered, and ethyl acetate was removed (30–40 mmHg). The crude ester was purified by chromatography over silica gel using mixture of hexane and ethyl acetate as the eluent. Methyl 2-chlorobenzoate, **3** (483 mg, 95% yield), was obtained as a colorless oil by

removing the solvents in vacuo. Only one peak was found in the GC, confirming its purity was >98%. ^{1}H NMR confirmed the structure.

Isopropyl 2-chlorobenzoate (4): NEt_3 (450 μL, 3.2 mmol) was added to a CH_2Cl_2 solution of 2-chlorobenzoyl chloride (525 mg, 3.0 mmol) and *iso*-propanol (250 μL, 198 mg, 3.3 mmol) at room temperature and kept overnight. The reaction solution was washed with water three times and dried over sodium sulfate. The solvent was evaporated under reduced pressure (30–40 mmHg). The residue was purified by chromatography over silica gel using a mixture of hexane and ethyl acetate as the eluent. A colorless oil, isopropyl 2-chlorobenzoate, **4**, (543 mg, 91% yield), was obtained by removing the solvents in vacuo. GC anaysis gave only a single peak confirming the purity of **4** was 97%. ^{1}H NMR confirmed the structure.

***t*-Amyl 2-chlorobenzoate (5):** *n*-BuLi (2.7 M, 1.1 mL, 3.0 mmol) was added to the THF solution of *t*-amyl alcohol (440 μL, 352 mg, 4.0 mmol) at −20°C. Then 2-chlorobenzoyl chloride (525 mg, 3.0 mmol) was added at −20°C. The following day the solvent was removed to give a solid that was dispersed into 3.0 mL water followed by extraction with ethyl acetate. After drying over sodium sulfate, the solvent was removed at 30–40 mmHg. The residue was chromatographed over silica gel using hexane/ethyl acetate mixtures as the eluent. A colorless liquid, *t*-amyl 2-chlorobenzoate, **5** (608 mg, 90% yield), was obtained by removing the solvents. The GC purity was >97%. ^{1}H NMR confirmed the structure.

The other esters (methyl octanoate, **9**, isopropyl octanoate, **10**, *t*-amyl octanoate, **11**, methyl cinnamate, **16**, isopropyl cinnamate, **17**, *t*-amyl cinnamate, **18**, methyl 3,4,5-trimethoxybenzoate, **21**, isopropyl 3,4,5-trimethoxybenzoate, **22**, *t*-amyl 3,4,5-trimethoxybenzoate, **23**) were synthesized using similar procedures. In every case their GC-determined purities exceeded 96–97%. ^{1}H NMR confirmed their structures.

Typical Procedure for the Reduction of Carboxylic Acids and Carboxylic Esters in $NaBH_4$/Diglyme at 162°C

Reduction of benzoic acid in $NaBH_4$/diglyme at 162°C: Sodium borohydride (75 mg, 2.0 mmol) was added to a refluxing diglyme (10 mL) solution of benzoic acid, **1**, (244 mg, 2.0 mmol) at 162°C. After 1 h, an aliquot was withdrawn, quenched with 15% (w/w) H_2SO_4 and analyzed by GC. The starting material was consumed completely. Quenching the reaction mixture with 15% H_2SO_4 gave a very low total isolated yield, because the diglyme can dissolve in water, making workup very difficult.

After several attempts, an effective method was found for product isolation.

After the reaction was finished, most of the diglyme was evaporated under reduced pressure (10–15 mmHg) and collected for recycle (to evaluate the feasiblity of reusing diglyme in large scale reactions). The residue was dissolved in a little water and 15% H_2SO_4 was used to bring the pH value to about 7. This solution was extracted with ethyl acetate. The ethyl acetate solution was dried over sodium sulfate and the ethyl acetate was removed at 30–40 mmHg. The residue was chromatographed column over silica gel (to remove any impurities) using hexane/ethyl acetate as the elutant. Benzyl alcohol, **6** (178 mg, 82% yield) was obtained as a colorless liquid (single GC peak) by removing the solvents in vacuo. ^{1}H NMR confirmed its structure.

Reductions of 3,4,5-trimethoxybenzoic acid (20) and *t*-amyl 3,4,5-trimethyoxybenzoates (23): A diglyme (5.0 mL) solution of 3,4,5-trimethoxybenzoic acid (424 mg, 2.0 mmol) was heated to 162°C, and then sodium borohydride (74 mg, 1.0 mmol) was added after the temperature reached to 162°C. After one hour, an aliquot was withdrawn and quenched with 15% (w/w) H_2SO_4, and the solution was analyzed with GC. Only the starting acid was found. No 3,4,5-trimethyoxybenzyl alcohol, **24**, had formed. After 8 h, no alcohol was generated.

3,4,5-Trimethyoxybenzyl alcohol was produced in 85% yield after 5 h (Table 5) when one equivalent of LiCl was added (per equivalent of substrate) to an otherwise identical reaction before heating the solution to 162°C. The other conditions were the same as the described above in the reduction carried out in the absence of LiCl.

The reduction of *t*-amyl 3,4,5-trimethoxybenzoate did not take place without added LiCl in the presence of one equivalent of $NaBH_4$ at 162°C.The *t*-amyl ester remained unchanged after 5 h at 162°C. If one equivalent of LiCl was added, 3,4,5-trimethyoxy benzyl alcohol was produced in 81% yield in 5 h.

2-Chlorobenzoic acid, **2**, octanoic acid, **8**, cinnamic acid, **15**, and esters **3**–**5**, **9**–**11**, **16**–**18**, and **21** and **22** were subjected to $NaBH_4$ reduction in a similar manner.

Spectra Data

All compounds listed below were obtained in sufficient purity to give a single GC peak and no impurity peaks were observed in the NMR except for **8**, **12**–**14** which were obtained as a single product mixture and identified by GC–MS and compared to standards.

Methyl 2-chlorobenzoate (3): Colorless liquid, ^{1}H NMR (300 MHz), $\delta_H(CDCl_3)$: 7.81 (1H, m), 7.42 (2H, m), 7.29 (1H, m), 3.91 (3H, s).

Isopropyl 2-chlorobenzoate (4): Colorless liquid, ^{1}H NMR (300MHz), $\delta_H(CDCl_3)$: 7.75 (1H, m), 7.41 (2H, m), 7.29 (1H), 5.29 (1H, m, $J = 6.26$ Hz), 1.37 (6H, d, $J = 6.27$Hz).

***t*-Amyl 2-chlorobenzoate (5):** Colorless liquid, ^{1}H NMR (300 MHz), δ_H ($CDCl_3$): 7.73 (1H, m), 7.40 (2H, m), 7.28 (1H, m), 1.93 (2H, q, $J = 7.53$ Hz), 1.57 (6H, s), 0.97 (3H, t, $J = 7.52$ Hz).

Benzyl alcohol (6): Colorless liquid, ^{1}H NMR (300 MHz), δ_H ($CDCl_3$): 7.38–7.30 (5H, m), 4.68 (2H, s).

2-Chlorobenzyl alcohol (7): M.p. 68.5–70.0°C, ^{1}H NMR (300 MHz), $\delta_H(CDCl_3)$, 7.46 (1H, m), 7.35 (1H, m), 7.23 (2H, m), 4.77 (2H, s), 2.15 (1H, br. s).

Octanoic acid (8): GC/MS (EI): *m*/*z* 145 (M+1, 12%), 101 (M−CO_2H, 43%), 73 (70%), 60 (100%).

Methyl octanoate (9): Colorless liquid, ^{1}H NMR (300 MHz), $\delta_H(CDCl_3)$: 3.64 (3H, s), 2.28 (2H, t, $J = 7.45$ Hz), 1.60 (2H, m, $J = 7.30$ Hz), 1.27 (8H, m), 0.87 (3H, t, $J = 6.97$ Hz). GC/MS (EI): *m*/*z* 159 (M+1, 18%), 127 (13%), 87 (60%), 74 (100%).

Isopropyl octanoate (10): Colorless liquid, ^{1}H NMR (300 MHz), $\delta_H(CDCl_3)$: 4.98 (1H, m, $J = 6.26$ Hz), 2.24 (2H, t, $J = 7.38$ Hz), 1.59 (2H, m, $J = 7.34$ Hz), 1.26 (8H, m), 1.20 (6H, d, $J = 6.27$ Hz), 0.86 (3H, t, $J = 6.95$ Hz).

***t*-Amyl octanoate (11):** Colorless liquid, ^{1}H NMR (300 MHz), $\delta_H(CDCl_3)$: 2.20 (2H, t, $J = 7.37$ Hz), 1.77 (2H, q, $J = 7.52$ Hz), 1.56 (2H, m, $J = 7.32$ Hz), 1.40 (6H, s), 1.27 (8H, m), 0.86 (3H, t, $J = 7.57$ Hz).

Octanol 12: GC/MS (EI): *m*/*z* 130 (M^+, 1%), 112 (M − H_2O, 3%), 73 (50%), 69 (86%), 55 (100%).

2-Methoxyethyl octanoate (13): GC/MS (EI), *m*/*z* 203 (M+1, 25%), 171 (M − OCH_3, 12%), 127 (M − $C_7H_{15}CO$, 60%), 58 (100%).

2-(2-Methoxyethoxy)ethyl octanoate (14): GC/MS (EI): *m*/*z* 145 (M − $CH_3OC_2H_4OC_2H_4$, 100%), 127 (M − $C_7H_{15}CO$, 32%), 103 (8%), 83 (35%), 69 (30%), 55 (61%).

Methyl cinnamate (16): M.p. 33.5–35°C, ^{1}H NMR (300 MHz), $\delta_H(CDCl_3)$: 7.70 (1H, d, $J = 16.04$ Hz), 7.52 (2H, m), 7.38 (3H, m), 6.44 (1H, d, $J = 16.03$ Hz), 3.81 (3H, s).

Isopropyl cinnamate (17): Colorless liquid, ^{1}H NMR (300 MHz), $\delta_H(CDCl_3)$: 7.67 (1H, $J = 16.05$ Hz), 7.53 (2H, m), 7.39 (3H, m), 6.42 (1H, d, $J = 15.99$ Hz), 5.15 (1H, m, $J = 6.20$ Hz), 1.32 (6H, d, $J = 6.27$ Hz).

***t*-Amyl cinnamate (18):** Colorless liquid, ^{1}H NMR (300 MHz), $\delta_H(CDCl_3)$: 7.58 (1H, d, $J = 15.98$ Hz), 7.51 (2H, m), 7.38 (3H, m), 6.38 (1H, d, $J = 16.01$ Hz), 1.86 (1H, q, $J = 7.50$ Hz), 1.50 (6H, s), 0.93 (3H, t, $J = 7.47$ Hz).

Methyl 3,4,5-trimethoxybenzoate (21): M.p. 80–82°C, ^{1}H NMR (300 MHz), $\delta_H(CDCl_3)$: 7.29 (2H, s), 3.90 (12H, s).

Isopropyl 3,4,5-trimethoxybenzoate (22): M.p. 39–41°C, ^{1}H NMR (300 MHz), $\delta_H(CDCl_3)$: 7.28 (2H, s), 5.30 (1H, m, $J = 6.26$ Hz), 3.91 (6H, s), 3.89 (3H, s), 1.36 (6H, $J = 6.26$ Hz).

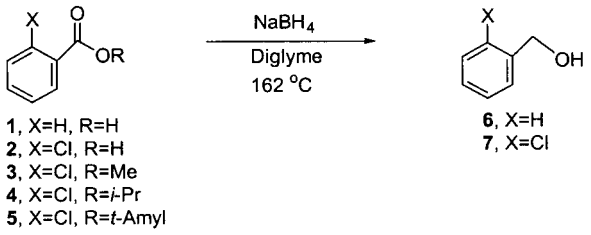
***t*-Amyl 3,4,5-trimethoxybenzoate (23):** Colorless oil, ^{1}H NMR (300 MHz), $\delta_H(CDCl_3)$: 7.25 (2H, s), 3.89 (6H, s), 3.88 (3H, s), 1.90 (2H, m, $J = 7.51$ Hz), 1.56 (6H, s), 0.97 (3H, t, $J = 7.46$ Hz).

3,4,5-Trimethoxybenzyl alcohol (24): (300 MHz), ^{1}H NMR $\delta_H(CDCl_3)$: 6.56 (2H, s), 4.59 (2H, s), 3.83 (6H, d, $J = 0.69$ Hz), 3.80 (3H, d, $J = 0.57$ Hz).

RESULTS AND DISCUSSION

Reduction of Aromatic Acids (1–2) and Esters (3–5) in $NaBH_4$/Diglyme at 162°C

The reductions of benzoic acid (**1**), 2-chlorobenzoic acids (**2**), and several alkyl 2-chlorobenzoates (**3–5**) with $NaBH_4$ in diglyme at 162°C gave good to excellent yields of benzyl alcohol or 2-chlorobenzyl alcohol, respectively (see Sch. 1). A good workup method for product isolation and solvent recycle was found. Representative reductions are shown in Table 1. Thus, raising the temperature to 162°C enables $NaBH_4$ to reduce these aromatic carboxylic acids to alcohols. Carboxylic acids are typically considered inert to $NaBH_4$ because the carboxylate anion is formed making hydride attack at the carbonyl carbon very difficult.



1, X=H, R=H
2, X=Cl, R=H
3, X=Cl, R=Me
4, X=Cl, R=*i*-Pr
5, X=Cl, R=*t*-Amyl

6, X=H
7, X=Cl

Scheme 1.

Table 1. Reductions of selected aromatic acids and esters with $NaBH_4$ in diglyme at 162°C.[a]

Entry	Substrate	Time (h)	$NaBH_4$/substrate (mole ratio)	Diglyme (mL)	Alcohol	
					Yield (%)[b]	Purity (%)
	Acids					
1	Benzoic, **1**	1	0.6	5	82	97
2	2-Chlorobenzoic, **2**	2	0.6	10	64[c]	97
3	2-Chlorobenzoic, **2**	2	0.6	5	84	96
4	2-Chlorobenzoic, **2**	2	1.0	10	87	97
	2-Chlorobenzoate dsters					
5	Me, **3**	1	0.6	5	86	97
6	*i*-Pr, **4**	2	0.6	5	92	97
7	*t*-Amyl, **5**	5	0.6	5	95	96

[a]2.0 mmol of substrate was used in each reaction.
[b]Yields are isolated yields. No carboxylic acid or ester substrate was present at the end of the reaction except in Entry 2. The product in Entry 1 is benzyl alcohol, **6**. In Entries 2–7, 2-chlorobenzyl alcohol, **7**, was produced.
[c]19% of the original 2-chlorobenzoic acid was recovered.

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

Table 2. Reductions of octanoic acid by $NaBH_4$ in diglyme at 162°C.[a]

Entry	$NaBH_4$/substrate (mole ratio)	Time (h)	Unreacted octanoic acid (%)	1-Octanol (%)
1	0.9	2.5	79	20
2	1.0	1.0	71	29
3	1.2	3.0	65	33
4	2.0	7.0	52	46

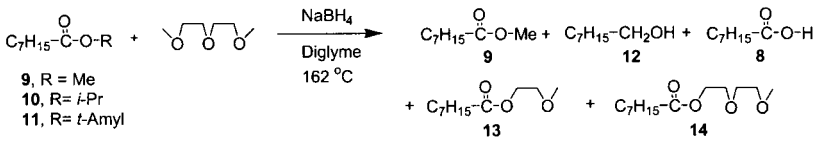
[a]No esters were observed which could have resulted from esterification of octanoic acid by alkoxide fragment from diglyme. The yields in columns 4 and 5 are from GC measurements.

Reduction of Octanoic Acid (8) and Alkyl Octanoates (9–11) in $NaBH_4$/Diglyme at 162°C

The reduction of octanoic acid to 1-octanol, **12**, by $NaBH_4$ in diglyme at 162°C does not occur easily. When the mole ratio of $NaBH_4$ to octanoic acid was increased from 0.9, 1.0, 1.2, and 2.0, the octanoic acid was never consumed completely. Even after 7.0 h at 162°C using a 2 mol excess of $NaBH_4$, 52% of the octanoic acid remained and only a 46% yield of octanol, **12**, was produced. When 1 equiv. of $NaBH_4$ was used, a 29% yield (GC) of octanol was obtained in 1 h (see Table 2) and using 0.9 equiv. of BH_4^- at 162°C for 2.5 h only produced 20% otanol. Using larger amounts of $NaBH_4$ and longer times usually gave higher alcohol yields. However, this did not always occur. The reaction mixtures are heterogeneous since the solubility of $NaBH_4$ in refluxing diglyme is only 0.43 g/100 g diglyme. Thus, the reaction may take place at $NaBH_4$ surfaces. Certainly, all the octanoic acid is present in solution as the carboxylate anion. Hydride attack on this carboxylate anion is very difficult since a dianion must result and this leads to a high activation energy in solution. Reductions on the surface may be favored by coordination of the dianion's oxygens with Na^+ ions of the solid. In all of these reactions, $NaBH_4$ was added to the substrate/diglyme solutions at 162°C.

In certain reactions, the $NaBH_4$ was added at temperatures between 100–130°C where the solubility of $NaBH_4$ is greater. However, improved yields were not obtained. Moreover, the addition of LiCl did not give improved alcohol yields.

Since reduction of octanoic acid, **8**, is slow, hydride attack on diglyme may compete at 162°C, giving alkoxide ions such as CH_3O^-, $CH_3OCH_2CH_2O^-$ etc. However, no esterification of octanoic acid was observed. The products were octanol, **12**, and unreduced octanoic acid, **8**.



Scheme 2.

$NaBH_4$ reductions of methyl, isopropyl, and *t*-amyl octanoate are shown in Sch. 2. Samples were summarized in Table 3. Surprisingly, the reduction of all three esters as very slow at 162°C. In reductions of **9** at a $NaBH_4$/methyl octanoate ratio of 0.65, no octanol was obtained after 5 h (Entries 1 and 2). Substantial amounts of this ester substrate remained in these reactions even when LiCl was added as a promoter. Since this reduction is slow, hydride attack on diglyme can compete to produce three alkoxide ions: CH_3O^-, $CH_3OCH_2CH_2O^-$, and $CH_3OCH_2CH_2OCH_2CH_2O^-$. These alkoxides react with the substrate to produce transesterification products **9**, **13**, and **14** (see Sch. 2) in addition to octanol. Methyl octanoate, **9**, undergoes transesterification with CH_3O^- so the remaining **9** in the reaction mixture cannot be distinguished from **9** formed by transesterification. However, formation of **9** during reactions of isopropyl and *t*-amyl octanoates, **10** and **11**, show that this transesterification proceeds (Entries 5–7, Table 3).

The complex product mixtures demonstrate that these $NaBH_4$ high temperature reductions are not suitable for reducing alkyl aliphatic esters to the corresponding alcohols. Aliphatic ester reductions were slower than those of benzoate esters. This result is the opposite of what is expected. Resonance delocalization between the phenyl ring and carbonyl group should slow the rate of hydride attack at carbonyl carbon of aromatic esters relative to that in aliphatic esters. The low rate of aliphatic ester reduction permits S_N2 attack by hydride on diglyme to compete (Sch. 3), producing alkoxide ions by cleavage of the solvent. The alkoxide ions produced then transesterify the original ester producing esters **9**, **13**, and **14**. LiCl addition (Entries 3 and 4, Table 3) would be expected to speed ester reduction by the coordination of Li^+ to the carbonyl oxygen, thereby enhancing the rate of hydride attack. However, Li^+ also enhances the rate of diglyme cleavage by BH_4^- at these high temperatures.

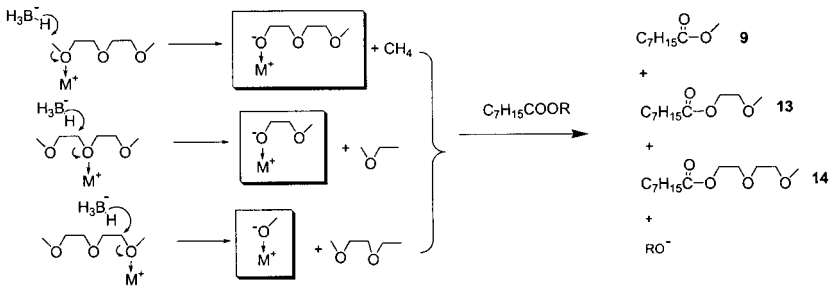
The presence of octanoic acid, **8**, observed in Entries 1–7 (Table 3) indicates that S_N1 or S_N2 substitution or E-2 elimination occurs, generating the carboxylate anion from the ester (Sch. 4). Upon workup, protonation gives octanoic acid. S_N1 and E-2 processes can't occur on methyl octanoate so S_N2 attack by hydride is involved. However, the observed 8% and 20% yields of octanoic acid, **8**, from *t*-amyl octanoate

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

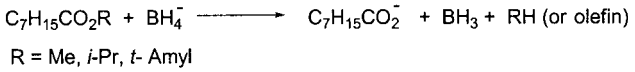
Table 3. $NaBH_4$ reduction of alkyl octanoates in diglyme at 162°C.

				Product yields[a]					
							Transesterification products		
Entry	Substrate $C_7H_{15}CO_2R$ (*R*)	$NaBH_4$/substrate (mole ratio)	Time (h)	Unreacted substrate[b] (%)	Octanol **12** (%)	Octanoic acid, **8** (%)	**9** (%)	**13** (%)	**14** (%)
1	Me, **9**	0.65	2.0	48[b]	0	1	48[b]	2	46
2	Me, **9**	0.65	5.0	14[b]	54	1	14[b]	1	27
3	Me, **9**	0.6 (0.5 LiCl)	2.0	55[b]	0	0	55[b]	16	20
4	Me, **9**	0.6 (0.5 LiCl)	5.0	27[b]	7	0	27[b]	7	53
5	*i*-Pr, **10**	0.65	7.0	31	16	3	5	11	24
6	*t*-Amyl, **11**	0.65	2.0	59	0	8	5	5	11
7	*t*-Amyl, **11**	0.65	6.0	47	0	20	3	6	16

[a]Yields are based on GC area percents for **13** and **14** for which internal standard-determined response factors were not available.
[b]Methyl octanoate could be either unreacted starting material or it could have come from hydride-induced cleavage of diglyme followed by transesterification. Thus, the amount formed by transesterification can't be distinguished.



Scheme 3.



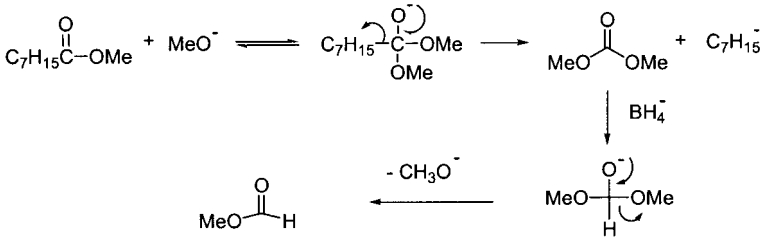
Scheme 4.

11 (Entries 6 and 7, Table 3) is more likely to result by an S_N1 or E-2 pathway. *t*-Amyl octanoate, **11**, is expected to reduce more slowly than its methyl or isopropyl analogs because of the *t*-amyl group's substantial steric effect. The *t*-amyl group should hinder nucleophilic attack at the carbonyl carbon. No octanol was observed in $NaBH_4$ reduction of **11**, consistant with this view. Slower reduction allows time for both transesterification to occur and octanoic acid to form. S_N2 substitution on **11** seems unlikely.

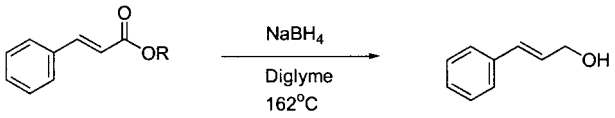
The transesterification products were identified by GC–MS. The amount of transesterification products increased with time from 2 h to 7 h. No esterification of octanoic acid with diglyme fragments took place during the octanoic acid reductions. When isopropyl octanoate is dissolved into the diglyme in the absence of $NaBH_4$ and then warmed to 162°C for 10 h, no other reaction products were observed (GC), confirming that sodium borohydride is necessary in the transesterification reactions.

Diglyme was heated with sodium borohydride at 162°C to study its stability at high temperature. Methanol is one of the products formed.

These high temperature $NaBH_4$ reductions of methyl octanoate also generated both methyl formate and methanol (identified by ^1H NMR). Methyl formate does not appear in reactions of diglyme with $NaBH_4$. The esters must be present. Methyl formate is postulated to arise from hydride attack on dimethyl carbonate (Sch. 5). Dimethyl carbonate could be envisioned to form by high temperature methoxide attack on methyl octanoate followed by occassional loss of $C_7H_{15}^-$ (Sch. 5).



Scheme 5.



15, R=H
16, R=Me
17, R=*i*-Pr
18, R=*t*-Amyl

19

Scheme 6.

Reductions of Cinnamic Acid (15) and Alkyl Cinnamates (16–18) with $NaBH_4$ in Diglyme at 162°C

The reductions of cinnamic acid and its methyl, **16**, isopropyl, **17**, and *t*-amyl, **18**, esters with $NaBH_4$ were investigated in diglyme at 162°C (Sch. 6). Cinnamic acid was converted to cinnamyl alcohol, **19**, in 67% yield (GC) after 7.0 h in the presence of 1 equiv. of $NaBH_4$ (Table 4, Entry 2). Only 3% of the cinnamic acid were remained and 30% of the material balance were unknown products. No reaction was observed in 2 h (Entry 1) but 97% of the acid was consumed in 7 h (Entry 2). This is reminiscent of methyl octanoate reduction (Entries 1 and 2) in Table 3. Again, such irregularities may signal that a heterogeneous reaction is occurring. Overall, exact rates were difficult to reproduce but the trends were consistent. Cinnamic acid was more readily reduced to alcohol than octanoic acid but more slowly reduced than benzoic and 2-chlorobenzoic acids.

Methyl cinnamate, **16**, can be reduced to cinnamyl alcohol, **19**, with $NaBH_4$ in diglyme at 162°C in about 65% yield (GC) after 3 h. Other products were also formed, but they were not studied. Only 2% of the

Table 4. Reductions of cinnamic acid and alkyl cinnamates by $NaBH_4$ in diglyme at 162°C.

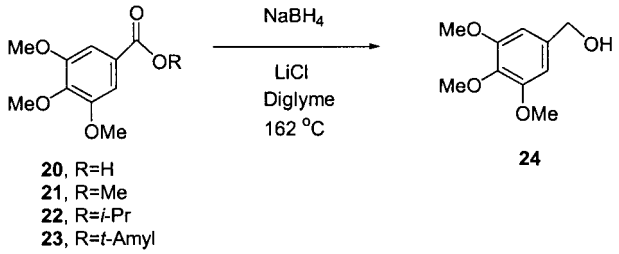
Substrate	Time (h)	$NaBH_4$/substrate (mole ratio)	Unreacted substrate (%)	Cinnamic alcohol (%)	Unknown products (%)
Cinnamic acid, **15**	2	0.9	100	0	0
Cinnamic acid, **15**	7	0.9	3	67	30
Methyl cinnamate, **16**	5	0.6	2	65	33
i-Propyl cinnamate, **17**	5	0.6	4	2	94
t-Amyl cinnamate, **18**	3	0.7	0	0	100

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

Table 5. Reductions of 3,4,5-trimethoxybenzoic acid and alkyl 3,4,5-trimethoxybenzoates in diglyme at 162°C with or without LiCl.[a]

Entry	*R*	$NaBH_4$/substrate (mole ratio)	Time (h)	Substrate remaining (%)	3,4,5-trimethoxy-benzyl alcohol (%)
1	H, **20**	1.0	8	100	0
2	H, **20**	1.0 with 1.0 equiv. LiCl	8	100	0
3	Methyl, **21**	0.6	5	100	0
4	Methyl , **21**	1.0 with 1.0 equiv. LiCl	5	0	85
5	*i*-Pr, **22**	0.6	5	100	0
6	*i*-Pr, **22**	1.0 with 1.0 equiv. LiCl	5	0	83
7	*t*-Amyl, **23**	1.0	5	100	0
8	*t*-Amyl ,**23**	1.0 with 1.0 equiv. LiCl	5	100	0

[a]Each reaction was run in 5 mL of diglyme using 2 mmol of benzoic acid or the esters.



Scheme 7.

starting material remained (GC). In contrast, reduction of isopropyl cinnamate with $NaBH_4$ gave only a 2% yield of cinnamyl alcohol at 96% ester conversion (Entry 4, Table 4). By-products represented 94% of the GC area. No cinnamyl alcohol was produced in 3 h from *t*-amyl cinnamate, **18**, using a $NaBH_4$/ester feed ratio of 0.7 although the ester was 100% consumed. Only unknown products were produced which were not studied (Entries 5, Table 4).

Reduction of 3,4,5-Trimethoxybenzoic Acid (20) and Alkyl 3,4,5-Trimethoxybenzoates (21–23)

Attempts to reduce reduced 3,4,5-trimethoxybenzoic acid, **20**, with $NaBH_4$ in diglyme produced no 3,4,5-trimethoxybenzyl alcohol, **24** (Table 5, Entries 1 and 2). Acid, **20**, was recovered unchanged after 8 h both in the presence or absence of 1 equiv. of LiCl. Apparently the three electron donating methoxy groups deactivate the 3,4,5-trimethyoxybenzoate anion to hydride attack at the carbonyl carbon relative to hydride attack on the carboxylate anions of benzoic and 2-chlorobenzoic acids (Sch. 7).

Methyl and isopropyl trimethoxybenzonates, **21** and **22**, also remained unreacted after treating with $NaBH_4$ for long periods in refluxing diglyme (Table 5, Entries 3 and 5). Furthermore, no transesterification products formed from diglyme cleavage. However, both **21** and **22** were reduced in good yields to 3,4,5-trimethoxybenzyl alcohol, **24** (85 and 83% yields respectively) in identical reactions (5 h) where an equivalent of LiCl was added (Entries 4 and 6). This illustrates the activating effect of the Li^+ cation. Finally, *t*-amyl 3,4,5-trimethoxybenzoate, **23**, did not react under these conditions even with LiCl present (Table 5, Entries 7 and 8). The larger steric bulk of the *t*-amyl group apparently retards the approach of BH_4^- to the carbonyl carbon. This, coupled with the electron

rich nature of the system, slows reduction. No 3,4,5-trimethoxybenzoic acid was formed. Thus, S_N1, S_N2, or E-2 reactions of the *t*-amyl ester do not occur, in contrast to the behavior of *t*-amyl octanoate.

SUMMARY

Diglyme is a good solvent for the reduction of aromatic acids and esters with $NaBH_4$ at 162°C to give corresponding alcohols. High temperatures increase the range of functional groups which $NaBH_4$ can reduce. Diglyme is not as good a solvent for the reduction of aliphatic esters due to the formation of transesterification products. Aliphatic acids and esters form alcohols, but diglyme cleavage competes. This leads to the formation of transesterification products. Aliphatic esters, surprisingly, reduce more slowly than aromatic esters.

The very electron rich 3,4,5-trimethoxybenzoate esters and the parent acid cannot be reduced by $NaBH_4$ at 162°C. The methyl and isopropyl 3,4,5-trimethoxybenzoates are reduced when LiCl is added.

ACKNOWLEDGMENTS

The work was supported, in part, by the Morton Division of Rohm and Haas and the Grant Division of Ferro Corp.

REFERENCES

1. Raber, D.J.; Guida, W.C. Tetrabutylammonium borohydride. Borohydride reaction in dichloromethane. J. Org. Chem. **1976**, *41*, 690.
2. Corsano, S.; Piancetelli, G. Sodium borohydride reduction of glycidic esters and lactones. J. Chem. Soc., Chem. Comm. **1971**, 1106.
3. Seki, H.; Koga, K.; Matsuo, H.; Ohki, S.; Matsuo, I.; Yamada, S. Optically active amino acids. V. Synthesis of optically active α-amino alcohols by the reduction of α-amino acid esters with sodium borohydride. Chem. Pharm. Bull. **1965**, *13*, 995.
4. Hill, M.E.; Ross, L.O. Fluoronitro Alcohol Compounds. US Patent 3,783,144, January 1, 1974.
5. Meschino, J.A.; Bond, C.H. 2-Amino-5,6-dihydro-1,3-oxazines. The reduction of carbolic esters with sodium borohydride. J. Org. Chem. **1963**, *28*, 3129.

6. Brown, H.C.; Subba, R.B.C. Reduction of esters and other difficultly reducible groups by sodium borohydride. J. Am. Chem. Soc. **1955**, *77*, 3164.
7. Brown, H.C.; Subba, R.B.C. A new powerful reducing agent—sodium borohydride in the presence of aluminum chloride and other polyvalent metal halides. J. Am. Chem. Soc. **1956**, *78*, 2582.
8. Paul, R.; Joseph, N. Reduction of esters to alcohol with alkaline borohydrides. Bull. Soc. Chim. France **1952**, 550.
9. Heeres, J.; Backx, L.J.J.; Van Cutsem, J. Antimycotic imidazoles. 3. Synthesis and antimycotic properties of 1-[2-(aryloxalkyl)-2-phenylethyl]-1-*H*-imidazoles. J. Med. Chem. **1977**, *20*, 1516.
10. Johnston, D.B.R. 3-Acyl-2-Amino-5-Halo-6-(Substituted)-Pyrazine Antimicrobial Compounds. US Patent 4,512,991, April 23, 1985.
11. Subba, R.B.C. Enhanced reduction efficiency of sodium borohydride in the presence of titanium tetrachloride. Current Sci. (India) **1961**, *30*, 218.
12. Banerji, J.; Das, B. Synthesis of (±)-Gadain, a new lignan from *Jatropha Gossypifolia Linn* (Euphorbiaceae). Heterocycles **1985**, *23*, 661.
13. Takata, T.; Kuo, M.; Tamura, Y.; Kabe, Y.; Ando, W. Convenient synthesis of 1-aza-3-thiabicyclo[3.1.0]hexanes from L-cysteine. Chem. Lett. **1985**, 939.
14. Nokajima, Y.; Ogawa, T.; Nakazato, A.; Kumazawa, Y.; Soda, K. 3-Nitratopropanol. Jpn. Kokai Tokkyo Koho Patent 60,178,845, September 12, 1985.
15. Yang, C.; Pittman, C.U., Jr. Reductions of organic functional groups using $NaBH_4$ or $NaBH_4$/LiCl in diglyme at 125 to 162°C. Synth. Commun. **1998**, *28* (11), 2027.
16. Zhu, H.-J.; Lu, K.-T.; Sun, G.-R.; He, I.-B.; Li, H.-Q.; Pittman, C. U., Jr. Reduction of amides in diglyme at 162°C. New J. Chem. **2003**, *27*, 409.
17. Pittman, C.U., Jr.; Yang, C. Dechorination of polychlorobiphenyls using $NaBH_4$ and $NaBH_4$/LiCl at 120–130°C in glyme solvents. J. Haz. Mat. **2001**, *B82*, 299.

Received in the USA February 22, 2002