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Cangming Yang [a] & Charles U. Pittman Jr. [a]
[a] Department of Chemistry, University/Industry Chemical Research Center Mississippi State University, Mississippi, 39762
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REDUCTIONS OF ORGANIC FUNCTIONAL GROUPS USING $NaBH_4$ OR $NaBH_4$/LiCl IN DIGLYME AT 125 TO 162 °C

Cangming Yang and Charles U. Pittman, Jr.*

Department of Chemistry
University/Industry Chemical Research Center
Mississippi State University, Mississippi 39762

Abstract: Reduction of nitro, amide, carboxylate, ester and nitrile functional groups to $-NH_2$, $-CH_2NH_2$, $-CH_2OH$, $-CH_2OH$ and $-CH_2NCHPh$, respectively were achieved using $NaBH_4$ or $NaBH_4$/LiCl in diglyme at 125-162 °C. This greatly extends the range of functional group types which can be considered generally reducible by borohydride.

Sodium borohydride is considered a very mild reducing agent.[1] It only readily reduces aldehydes, ketones and acid chlorides (see Table 1). Since sodium borohydride is safe to use and rather inexpensive it would desirable to extend the range of functions which could be reduced by sodium borohydride. Methods used previously to modify $NaBH_4$ reactivity include (1) use of solvent effects (e.g., chelate effect in dipolar aprotic solvents such as dimethyl sulfoxide, sulfolane, and hexamethylphosphotriamide);[2,3] (2) exchange of sodium for another metal cation in the complex hydride (e.g. formation of

*To whom correspondence should be addressed

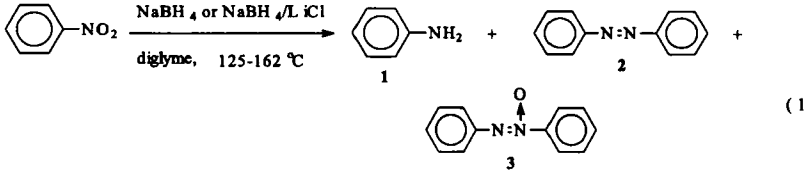
lithium borohydride *in situ* upon adding LiCl or LiBr to $NaBH_4$/diglyme solution);[4,5] (3) replacing hydride with alkoxy, or alkyl groups in the borohydride anion (e.g., formation of alkoxyborohydrides[6] or alkylborohydrides[7]). Other approaches include the development of acidic reducing agents such as borane[8] and alane[9] and the introduction of substituent groups into such acidic reducing agents.[10,11] Finally, other strong hydride reducing agents such as $LiAlH_4$ have been widely employed despite their lower stability and higher cost. However, despite sodium borohydride's high thermal stability, the simple expedient of extending its use to higher temperatures has largely been neglected. Therefore, in this paper the simultaneous use of elevated temperatures, added LiCl and glyme solvents were explored to attempt the reduction of aryl $-NO_2$, $-CONH_2$, -COOH, -CN and -COOR functional groups. Concurrent studies in our laboratory showed these media were also effective for both dechlorination[12] and defluorination[13] of aryl compounds. Heretofore, none of these functional groups have been generally considered reducible in BH_4^- reductions.

Reduction of nitrobenzene using $NaBH_4$, $NaBH_4$/LiCl, or $NaBH_4$/LiCl/NH_4Cl in diglyme

Nitrobenzene was reduced by 5 equivalents of sodium borohydride in diglyme at 162 °C. (see Table 2). Nitrobenzene totally disappeared within 5 min producing aniline (30%), azobenzene (8%), and azoxybenzene (38%) (Table 2, Entry 1 & Eq. 1). The products were analyzed by GC and GC/MS.

Table 1. Comparison of the reactivity of sodium borohydride with and without LiCl[14]

Substrate	Product upon treatment with $NaBH_4$/alcohol	Product upon treatment with $NaBH_4$/LiCl/diglyme
aldehyde	alcohol	alcohol
ketone	alcohol	alcohol
acid chloride	reaction with solvent	alcohol
lactone	*slow* reaction	glycol
epoxide	*slow* reaction	alcohol
ester	*slow* reaction	alcohol
carboxylic acid	carboxylate anion, *no reduction*	carboxylate anion, *no reduction*
carboxylic acid salt	*no reaction*	*no reaction*
tert-amide	*no reaction*	*no reaction*
nitrile	*no reaction*	*no reaction*
nitro	*no reaction*	*very slow reaction*
Aryl chloride	*no reaction*	*no reaction*
Aryl fluoride	*no reaction*	*no reaction*



(1)

The amount of aniline steadily increased with time (Table 2, Entries 1, 2, 3, and 4) while the amount of azoxybenzene decreased. The amount of azobenzene increased early during the reaction due to reduction of azoxybenzene and then decreased. The reaction proceeded no further after 12 h. Aniline was the major product (65% yield based on internal standard techniques) and azobenzene as the minor incomplete reduction product (12%).

Table 2. Reduction of nitrobenzene (1 mmol) using $NaBH_4$/diglyme (5 mmol/42 mmol) at 162 °C

Entry	Time (h)	Substrate Consumption (Mole%)	Products Identified (Mole%)[a]	
1	0.08	100	Aniline	30%
			Azobenzene	8%
			Azoxybenzene	38%
2	0.5	100	Aniline	35%
			Azobenzene	13%
			Azoxybenzene	30%
3	1.5	100	Aniline	38%
			Azobenzene	26%
			Azoxybenzene	13%
4	12	100	Aniline	65%
			Azobenzene	12%
			Azoxybenzene	0%
5	48	100	No further reaction	

[a] The yields were determined by internal standard method.

Addition of an equimolar amount LiCl to $NaBH_4$ in diglyme at 162 °C had little effect on the amount of nitrobenzene reduced or on the product distributions. The yield of aniline after 12 h was 67 %. Increasing both the $NaBH_4$/nitrobenzene and the LiCl/nitrobenzene mole ratios to 10 from 5 slightly increased the reduction rate giving a 70% yield of aniline in 10 h (azobenzene was present as a minor product). Dropwise addition of nitrobenzene (1 mmol) to the premixed $NaBH_4$/LiCl (5 mmol/5 mmol) in diglyme (42 mmol) at 162 °C gave a 68% yield of aniline after 11 h (azobenzene was again present as a minor product).

Table 3. Reduction of nitrobenzene (1 mmol) using $NaBH_4/LiCl/NH_4Cl$/diglyme (10/10/20/42) at 162 °C

Entry	Time (h)	Substrate Consumption (Mole%)	Products Identified (Mole%)[a]	
1	1/3	100	Aniline	58%
			Azobenzene	7%
			Azoxybenzene	18%
2	2	100	Aniline	71%
			Azobenzene	15%
			Azoxybenzene	0%
3	5	100	Aniline	97%
			Azobenzene	0%
			Azoxybenzene	0%

[a] The yields were determined by internal standard method.

In solvated electron reductions, nitro groups are more completely reduced and lower yields of reductive dimers are formed when a good proton source is available.[15] Therefore attempts were made to decrease the amount of reductive dimers (azobenzene, **2**, and azoxybenzene, **3**) formed by adding NH_4Cl as a proton source in a 20 mole excess over nitrobenzene. Adding NH_4Cl/nitrobenzene/diglyme portion-wise to premixed 10 mole excess of $NaBH_4/LiCl$(1:1) diglyme solution gave smaller amounts of reductive dimers **2** and **3** which were quickly reduced to aniline (Table 3). The yield of aniline (bp 183-184°C) was 97% in 2.5 h. Decreasing the $NaBH_4/LiCl/NH_4Cl$ to substrate ratio from 10/10/20 to 5/5/10 resulted in slower reduction rates and the more azobenzene production (not listed).

Table 4. Reduction of benzamide (1 mmol) using $NaBH_4$/diglyme (4/42) at 162 °C

Entry	Time (h)	Benzamide Consumption (Mole%)	Benzylamine Formation (Mole%)[a]
1	0.33	51	50
2	1	68	68
3	1.5	100	99

[a] Benzylamine was the only reduction product detected. The yields were determined by the internal standard method.

Reduction of benzamide using $NaBH_4$ in diglyme

Benzamide was readily reduced to benzylamine using $NaBH_4$ alone in diglyme at 162 °C (reflux). Example results are shown in Table 4. Benzamide was 51% consumed in 20 min (Entry 1, Table 4), 68% reacted in 1 h (Entry 2) and benzamide was completely gone within 1.5 h. Benzylamine was the only observed product. The product was characterized by GC and GC/MS versus authentic benzylamine and isolation by distillation (bp 183-184°C).

The yield of benzylamine was 99% (IS technique).

Reduction of benzoic acid using $NaBH_4$ or $NaBH_4$/LiCl in diglyme

Benzoic acid was reduced to benzyl alcohol using either $NaBH_4$/diglyme or $NaBH_4$/LiCl/diglyme at 162 °C. The results are shown in Tables 5 and 6. Benzoic acid was 58%, 86% and 100% consumed in 4 h (Entry 1, Table 5), 10 h (Entry 2) and 15 h (Entry 3), respectively using $NaBH_4$/diglyme. Benzyl alcohol was the sole product. Benzyl alcohol was characterized by GC, GC/MS

Table 5. Reduction of benzoic acid (1 mmol) using $NaBH_4$/ diglyme (7.5 mmol/42 mmol) at 162 °C

Entry	Time (h)	Benzoic acid Consumption (Mole%)	Benzyl alcohol Formation (Mole%)[a]
1	4	54	52
2	9	86	85
3	15	100	98

[a] Benzyl alcohol was the only reduction product detected. The yields were determined by the internal standard method.

Table 6. Reduction of benzoic acid (1 mmol) using $NaBH_4$/LiCl/diglyme (7.5/7.5/42) at 162 °C

Entry	Time (h)	Benzoic acid Consumption (Mole%)	Benzyl alcohol Formation (Mole%)[a]
1	4	27	26
2	9	75	73
3	15	100	97

[a] Benzyl alcohol was the only reduction product detected. The yields were determined by the internal standard method.

versus authentic samples, and distillation (bp 204-205°C). Addition of an equimolar amount LiCl to $NaBH_4$/diglyme lowered the reduction rates somewhat. Thus, a 73% yield (Entry 2, Table 6) of benzyl alcohol was obtained in 9 h and 97% yield (Entry 3, Table 6) in 15 h.

The carboxyl group is present as its carboxylate anion in the presence of borohydride, demonstrating the strong reducing potential of these media at elevated temperatures.

Table 7. Reduction of benzyl benzoate (1 mmol) in $NaBH_4$/ diglyme (4/42) at 162 °C

Entry	Time (h)	Benzyl benzoate Consumption (Mole%)[a]	Benzyl alcohol Produced (Mole%)[a]
1	1/6	47.3	46
2	1/2	71.8	71
3	1	87.3	87
4	2	99.5	99

[a] Benzyl alcohol was the only reduction product detected. The yields were determined by internal standard method.

Reduction of Benzyl benzoate using $NaBH_4$ in diglyme

Benzyl benzoate was readily reduced to benzyl alcohol using $NaBH_4$ alone in diglyme at 162 °C (reflux). Example results are summarized in Table 7. Benzyl benzoate was 47% consumed within 10 min (Entry 1, Table 7), 71.8% in 0.5 h (Entry 2), 87.3% in 1 h (Entry 3) and 99.5% within 2 h. A 99% yield of benzyl alcohol was achieved in 2 h (IS technique). Benzyl alcohol was characterized by GC and GC/MS versus authentic samples.

Reduction of benzonitrile using $NaBH_4$ or $NaBH_4$/LiCl in diglyme

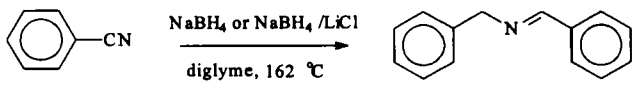
Benzonitrile reductions were attempted using several conditions summarized in Table 8. Benzonitrile slowly disappeared when $NaBH_4$/diglyme was used at 162 °C. Only 35% of the benzonitrile was consumed after 24 h (Entry 1, Table 8). Benzyl amine, however was not produced. The dimeric product, N-benzylidenebenzylamine, was produced and characterized by

Table 8. Reduction of benzonitrile using $NaBH_4$ or $NaBH_4$/LiCl in diglyme

Entry	Reagents (Mol Ratios)[a]	Temp (°C)	Time (h)	Benzonitrile Consumption (Mole%)[a]	N-benzylidene benzylamine (Mole%)
1	$NaBH_4$/diglyme 5/42	162	24	35	31
2	$NaBH_4$/LiCl/diglyme 5/5/42	162	2	26	
			10	86	
			14	100	90
3[b]	$NaBH_4$/LiCl/diglyme 5/5/42	125	1	57	
			2	89	
			3	100	91

[a] All the ratios are relative to one mole of benzonitrile. The yields were determined by internal standard method. [b] The reaction mixture was stirred for 20 minutes before heating at 125 °C.

GC/MS vs an authentic sample (Eq. 2). Saturated dimeric product (dibenzyl amine) was excluded by spiking authentic samples.



(2)

Benzonitrile was consumed faster when LiCl was added to $NaBH_4$/diglyme at 162 °C, completely disappearing to give a 90% yield of N-benzylidenebenzylamine (Entry 2). Benzonitrile disappeared much more rapidly (within 3 h) when the $NaBH_4$/LiCl/diglyme reaction mixture was stirred first at room temperature and then heated to only 125 °C (a 91% yield of N-benzylidenebenzylamine was produced)(Entry 3).

In conclusion, aryl functions including nitro, amide, carboxyl, ester and nitrile were readily reduced by $NaBH_4$ or $NaBH_4$/LiCl in diglyme at 125-162°C.

Experimental

General Procedure Reduction of nitrobenzene (Table 2). Diglyme (6 mL, 42 mmol), nitrobenzene (0.1244 g, 1 mmol) and tetradecane (IS, 100 ul) were added into an oven-dried, 50 mL three-necked flask equipped with stirring bar, thermometer, septa and reflux condenser. After stirring and preheating the mixture to 162 °C (reflux), $NaBH_4$ (0.192 g, 5 mmol) was added. Aliquotes (0.1 mL) of the reaction mixture was withdrawn by a syringe at appropriate time intervals, quenched with dilute H_2SO_4, made basic with 20% aq. NaOH solution to pH=9 (alternatively, quenched in aq. ammonium chloride solution (pH=8.5)), extracted with CH_2Cl_2 and analyzed by GC. The GC temperature program and conditions employed in the analyses were: 30 m, DB-5 capillary column, FID detector; 80 °C, 2 min, with subsequent heating at 20 °C/min to 300 °C where it was held for 5 min. Aniline (MS, m/z = 93 molecular ion; the fragmentation pattern identical to that of authentic aniline) was produced in 65% yield after 12 h along with azobenzene as a minor product.

Reduction of nitrobenzene (Table 3). A mixture of nitrobenzene (0.1244 g, 1 mmol), NH_4Cl (1.08 g, 20 mmol) and diglyme (2 mL, 14 mmol) was added portion-wise into a solution of LiCl (0.424 g, 10 mmol), $NaBH_4$ (0.384 g, 10 mmol), diglyme (4 mL, 28 mmol) and tetradecane (IS, 100 ul) at 162 °C. The sampling procedures and analysis were the same as described for Table 2.

Aniline was produced (97%) as the only detected reduction product after 2.5 h. Scaling up this reaction to 12g of nitrobenzene in 70 ml of diglyme (substrate/NH_4Cl/LiCl/$NaBH_4$ = 1/20/10/10 mole equivalents) followed by ether/water partitioning, drying of the ether layer and distillation gave 8.1 g of aniline (bp 183-184°C).

Reduction of Benzamide (Table 4, entry 3). $NaBH_4$ (0.154 g, 4.0 mmol), diglyme (6 mL, 42 mmol), benzamide (0.121g, 1 mmol) and octadecane (IS, 100 μl) were reacted at 162°C. After 1.5 h GC analysis indicated a 99% yield of benzylamine (only product detected) and the benzamide was totally consumed. The reaction mixture was quenched in aqueous NH_4Cl (pH = 8.5) and extracted into methylene chloride. Benzylamine was isolated by removing solvent and its structure confirmed by GC spiking studies (with an authentic commerical sample at three different temperature programs) and its mass spectrum was identical with that of a commercial sample (molecular ion at m/z = 107). A 15-fold scale up procedure was carried out and the resulting benzyl amine was isolated by distillation (bp 183-184°C).

Reduction of Benzoic Acid (Table 5, entry 3). $NaBH_4$ (0.288g, 7.5 mmol) was added to a stirred solution of diglyme (6 mL, 42 mmol), benzoic acid (0.123g, 1 mmol) and tetradecane (IS, 100 μl) at 162°C. After 15 h an aliquote was analyzed by GC. No benzoic acid was detected. The only product observed was benzyl alcohol (98% yield based on internal standard method). The benzyl alcohol was then worked up by quenching into dilute sulfuric acid

and extraction into methylene chloride. Its structure was confirmed by a GC spiking experiment versus authentic benzyl alcohol (3 conditions) and its mass spectrum was identical to that of an authentic sample (molecular ion at m/z = 106; parent ion was the $C_7H_7^+$ ion at m/z = 89). A 12-fold scale up reaction provided an isolated benzyl alcohol (distilled bp 204-205°C) yield of 71%.

Reduction of Benzyl Benzoate (Table 7, entry 4). $NaBH_4$ (0.154 g, 4 mmol) was added into a stirred solution of diglyme (3 mL, 21 mmol), benzyl benzoate (0.0186 g, 1 mmol), tetradecane (IS, 100 μl) at 162°C. After 2h, GC analysis showed 99.5% of the ester had been consumed and a 99% yield of benzyl alcohol formed. No other product was observed. The reaction mixture was quenched into dilute aqueous sulfuric acid (~5% wt) and then extracted with methylene chloride. Benzyl alcohol was confirmed as the product by GC spiking and by mass spectrometry as is described in the preceeding example.

Reduction of Benzonitrile (Entry 3, Table 8). LiCl (0.212 g, 5 mmol), and $NaBH_4$ (0.192 g, 5 mmol) were added to a solution of benzonitrile (0.103 g, 1 mmol) and tetradecane (IS, 100 ul), diglyme (6 mL, 42 mmol). The reaction mixture was prestirred at room temperature for 20 min before heating at 130 °C. The sampling procedures and analyses were the same as described for Table 2. Total consumption (100%) of benzonitrile occurred within 3 h, producing a 91% yield of N-benzylidenebenzylamine. Two workup procedures were used: (a) quench in 5% H_2SO_4 and then raise pH to 10 with aqueous NaOH and extract into methylene chloride; (b) quench into aqueous NH_4Cl at

pH = 8.5 and extract with methylene chloride. The identity of the product was confirmed by several GC spiking experiments (different temperature programs) with authentic commercial N-benzylidene benzylamine. Furthermore, dibenzylamine was excluded by GC spiking experiments. MS of the product exhibited a molecular ion at m/z = 195 and the MS fragmentation pattern was identical to that of a commercial sample of N-benzylidene benzylamine.

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