

# Sodium borohydride reduction of ketones, aldehydes and imines using PEG400 as catalyst without solvent

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**Abstract:** Aldehydes, ketones and imines were readily reduced by sodium borohydride, with the participation of a small amount of water, in good to excellent yields using PEG400 as catalyst in the absence of organic solvents.

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**Keywords:** reduction; carbonyl compounds; imines; sodium borohydride; PEG400; solventless

## INTRODUCTION

Sodium borohydride, as a kind of common reductant, has been used widely in organic synthesis.<sup>1,2</sup> Reduction of liquid or solid ketones and aldehydes using sodium borohydride or potassium borohydride in alcohol or water solvent is a general and efficient procedure to prepare alcohols.<sup>3–5</sup> Recently, solid state reduction of ketones and aldehydes using sodium borohydride has been reported.<sup>6</sup> However, the obvious drawbacks of these solid phase reductions are that the process needs the reaction flask to be shaken for a day,<sup>7</sup> or microwave irradiation that, up to now, only allows preparation on a small scale.<sup>8</sup> Reduction of imines is an important method of preparing secondary or tertiary amines<sup>9</sup> and sodium borohydride or retouched sodium borohydride can efficiently reduce imines.<sup>10</sup> Most reductions were carried out in organic solvents,<sup>11</sup> therefore we want to investigate a new process without the use of organic solvent.

As is known, solvent-free organic synthesis has great value and expansive prospects.<sup>12</sup> In recent years, polyethylene glycols (PEGs) of various molecular weights have found a lot of industrial application as phase-transfer catalysts (PTC) or as acyclic crown ether analogs.<sup>13,14</sup> PEG400, with a middle molecular weight, is always selected as a desirable phase-transfer catalyst in non-aqueous heterogeneous reactions. The attractive features of PEG400 include its low cost, stability, ready availability and apparent lack of significant toxicological properties. In addition, compared with crown ether and quaternary ammonium salts, it has a more powerful ability to solubilize inorganic salts due to the fact that they have terminal polar hydroxyl groups, which play important roles in attacking the crystal lattice of the solid.

In the continuation of our research on the use of PEGs as PTC in organic synthesis without solvent,<sup>15–17</sup> we now report a facile method for the preparation of alcohols and amines by sodium borohydride reduction of aldehydes, ketones and imines using PEG400 as PTC (see Scheme 1).

## EXPERIMENTAL

Thin layer chromatography (TLC) was carried out with GF<sub>254</sub> as adsorbent and petroleum ether/diethyl ether (2/1) as eluent. Liquid ketones or aldehydes were distilled before use.

### Reduction of acetophenone

A mixture of acetophenone (0.1 mol), H<sub>2</sub>O (0.2 mol), and PEG400 (1.5 mL) were put into a 50 mL three-necked, round-bottomed flask equipped with a mechanical stirrer. After stirring for 10 min, NaBH<sub>4</sub> (0.05 mol) was added for 20 min. Then the mixture was vigorously stirred at room temperature. The progress of the reaction was monitored by TLC. The reaction mixture was washed with water three times. The organic phase was separated, dried over magnesium sulfate and then distilled under reduced pressure to give pure alpha-methylbenzyl alcohol. Identification was based on comparison of physical data.

### Reduction of *N*-benzylideneaniline

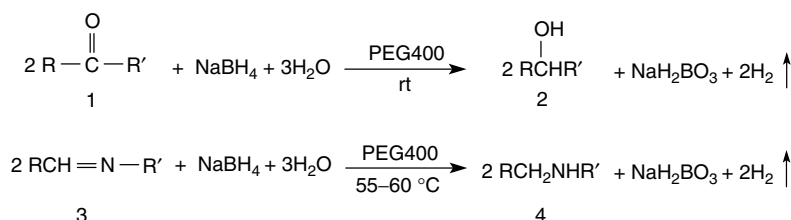
A mixture of *N*-benzylideneaniline (0.1 mol), H<sub>2</sub>O (0.2 mol), and PEG400 (1.5 mL) was put into a 50 mL three-necked, round-bottomed flask equipped with a mechanical stirrer. After stirring for 10 min, NaBH<sub>4</sub> (0.05 mol) was added for 20 min. Then the mixture

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**Scheme 1.** Reduction of aldehydes, ketones and imines.

was vigorously stirred at 55–60 °C. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature and was washed with water three times. The product was filtered, dried, recrystallized from ethanol to give pure *N*-phenylbenzylamine. Identification was based on comparison of physical data.

## RESULTS AND DISCUSSION

As shown in Table 1, several structurally different ketones and aldehydes underwent reduction to corresponding alcohols in excellent yields, and aliphatic ketones, alicyclic ketones and aromatic aldehydes can be reduced in a relatively shorter time than aromatic ketones owing to the higher activity of carbonyl groups. Also, the aromatic ketones or aldehydes with electron-withdrawing groups, such as –Cl, –Br, in the aromatic ring are more reactive than those with electron-donating groups such as –OCH<sub>3</sub>. The carbonyl group of  $\alpha$ ,  $\beta$ -unsaturated ketones or aldehydes was selectively reduced by NaBH<sub>4</sub> while the double bond was retained. However, ketones or aldehydes with –OH groups in the aromatic ring could

be reduced by NaBH<sub>4</sub> under these conditions because they formed sodium phenolates. According to Table 1, a longer reaction time and higher reaction temperature were needed in the reduction of imines than ketones or aldehydes, but the reaction temperature could not exceed 70 °C because more NaBH<sub>4</sub> would be hydrolyzed at higher temperature. Lower yields were obtained because the imine group was less active than the carbonyl group because of the formation of some by-products. The easier reduction of imine ‘u’ (Table 1) than other aryl imines may be due to the steric effect of the aryl ring.

Using PEG400 as a phase-transfer catalyst in the reaction allowed us to perform the condensation under mild conditions and obtain a higher yield. The optimum amount of PEG400 was between 3 and 4% (mole ratio of PEG400 to substrate). A longer reaction time was needed and a lower yield was obtained with less PEG400.

A small amount of water may accelerate the reaction by providing protons and hydrolyzing the boric acid ester formed in the reaction. Taking the reduction of acetophenone as an example, the effect of the amount of NaBH<sub>4</sub> and water on the reaction was

**Table 1.** Reduction of ketones, aldehydes or imines using sodium borohydride and PEG400

Entry	Ketone, aldehyde or imine	Alcohol or amine	Time (min)	Yield (%)	MP(°C) or BP(°C/mmHg)	
					Found	Lit
a	CH <sub>3</sub> COCH <sub>3</sub>	CH <sub>3</sub> CH(OH)CH <sub>3</sub>	30	94	81–82/760	82/760 <sup>18</sup>
b	CH <sub>3</sub> CH <sub>2</sub> COCH <sub>3</sub>	CH <sub>3</sub> CH <sub>2</sub> CH(OH)CH <sub>3</sub>	40	97	99/760	100/760 <sup>18</sup>
c	(CH <sub>3</sub> ) <sub>2</sub> CHCOCH <sub>3</sub>	(CH <sub>3</sub> ) <sub>2</sub> CHCH(OH)CH <sub>3</sub>	50	96	111–112/760	112/760 <sup>19</sup>
d	Cyclopentanone	Cyclopentanol	40	98	139/760	140/760 <sup>18</sup>
e	Cyclohexanone	Cyclohexanol	50	97	160–161/760	161/760 <sup>18</sup>
f	C <sub>6</sub> H <sub>5</sub> COCH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub> CH(OH)CH <sub>3</sub>	90	96	97–98/20	98/20 <sup>19</sup>
g	<i>p</i> -BrC <sub>6</sub> H <sub>4</sub> COCH <sub>3</sub>	<i>p</i> -BrC <sub>6</sub> H <sub>4</sub> CH(OH)CH <sub>3</sub>	50	98	127–128/10	128/10 <sup>20</sup>
h	<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> COCH <sub>3</sub>	<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CH(OH)CH <sub>3</sub>	120	94	121/8	122/8 <sup>20</sup>
i	(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> C=O	(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> CHOH	110	93	66–67	65–67 <sup>18</sup>
j	(C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> ) <sub>2</sub> C=O	(C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> ) <sub>2</sub> CHOH	70	92	197–198/20	198/20 <sup>19</sup>
k	C <sub>6</sub> H <sub>5</sub> CH=CHCOCH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub> CH=CHCH(OH)CH <sub>3</sub>	100	95	39–40	39–41 <sup>19</sup>
l	C <sub>6</sub> H <sub>5</sub> CH=CHCOC <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub> CH=CHCH(OH)C <sub>6</sub> H <sub>5</sub>	120	94	53–54	54–55 <sup>20</sup>
m	C <sub>6</sub> H <sub>5</sub> CHO	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> OH	40	96	204–205/760	205/760 <sup>18</sup>
n	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub> CHO	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> OH	30	96	164–165/16	165/16 <sup>18</sup>
o	<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CHO	<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> OH	90	93	140–141/20	141/20 <sup>18</sup>
p	Furfural	Furfuryl alcohol	90	94	169–170/760	170/760 <sup>19</sup>
q	C <sub>6</sub> H <sub>5</sub> CH=CHCHO	C <sub>6</sub> H <sub>5</sub> CH=CHCH <sub>2</sub> OH	70	96	141–142/20	142/20 <sup>19</sup>
r	C <sub>6</sub> H <sub>5</sub> CH=NC <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> NHC <sub>6</sub> H <sub>5</sub>	240	89	36–38	35–38 <sup>19</sup>
s	<i>p</i> -BrC <sub>6</sub> H <sub>4</sub> C(CH <sub>3</sub> )NC <sub>6</sub> H <sub>5</sub>	<i>p</i> -BrC <sub>6</sub> H <sub>4</sub> CH(CH <sub>3</sub> )NHC <sub>6</sub> H <sub>5</sub>	210	88	75–76	76 <sup>20</sup>
t	<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CH=NC <sub>6</sub> H <sub>5</sub>	<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> NHC <sub>6</sub> H <sub>5</sub>	250	88	58–59	59 <sup>19</sup>
u	C <sub>6</sub> H <sub>5</sub> CH=NCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> NHCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	180	92	171–172/20	172/20 <sup>19</sup>

**Table 2.** Effect of the amount of NaBH<sub>4</sub> and water on the reaction

Acetophenone(mol)	NaBH <sub>4</sub> (mol)	H <sub>2</sub> O(mol)	Time(h)	Yield(%)
0.04	0.04	0	24	35
0.04	0.015	0.04	7	80
0.04	0.015	0.16	4	86
0.04	0.02	0.08	1.5	96
0.04	0.04	0.08	1.2	96

investigated. The results are summarized in Table 2. It was found that the reaction could not be accomplished without water over a long reaction time even though the amount of NaBH<sub>4</sub> was much more than the theoretical amount. The optimal mole ratio of NaBH<sub>4</sub>, acetophenone and water is 1:2:4.

## CONCLUSION

Here we have reported a new procedure for the reduction of some ketones, aldehydes and imines. The advantages offered by this procedure include higher yield, operational simplicity, low cost, less pollution of the environment and easy application in industrial processes.

## REFERENCES

- Bruce G and John OO, Synthetically useful reactions with metal boride and aluminide catalysts. *Chem Rev* **86**:763–780 (1986).
- Gribble GW, Sodium borohydride in carboxylic acid media: a phenomenal reduction system. *Chem Soc Rev* **27**:395–404 (1998).
- Ege SN, *Organic Chemistry*, 3rd edn, DC Heath and Co-Lexington, Boston, pp 510–517 (1994).
- Chamberlin AR and Daniel JS, *Comprehensive Organic Synthesis*, 3rd edn, Pergamon Press, New York, 923–927 (1991).
- Caycho JR, Tellado FG, Armas PD and Tellado JJM, Sodium borohydride-amberlyst-15 (H<sup>+</sup>): an effective reductor for hindered and unreactive ketones in aprotic solvent. *Tetrahedron Lett* **38**:277–280 (1997).
- Liu WY, Xu QH and Ma YX, Silica gel promoted solvent-free synthesis of arylcarbinols and ferrocenylcarbinols. *Org Prep Proced Int* **32**:596–601 (2000).
- Toda F, Kiyoshige K and Yagi M, NaBH<sub>4</sub> reduction of ketones in the solid state. *Angew Chem Int Ed Engl* **28**:320–321 (1989).
- Varma RS and Saini RK, Microwave-assisted reduction of carbonyl compounds in solid state using sodium borohydride supported on alumina. *Tetrahedron Lett* **38**:4337–4338 (1997).
- Zhao B, Wang FQ and Xia M, Synthesis of new aza-crown ethers containing pyridine ring and their liquid membrane transport of alkali cations. *Chin Chem Lett* **12**:31–35 (2001).
- Akisanya J, Danks TN and Garman RN, Reaction of (1-azabuta-1,3-diene)tricarbonyliron(0) complexes with sodium borohydride under microwave conditions. *J Organomet Chem* **603**:240–246 (2000).
- Titcomb L, Reduction of an imine to an amine: *N,N'*-bis-(2,6-diisopropylphenylamine)ethane dihydrochloride. *Synthetic Page* **16**:30–34 (2001).
- Tanaka K and Toda F, Solvent-free organic synthesis. *Chem Rev* **100**:1025–1073 (2000).
- Wang XC, Li Z, Da YX and Chen JC, Phase transfer catalyzed synthesis of 4-carboxyl-phenoxyacetic acid derivatives. *Synth Commun* **29**:4153–4159 (1999).
- Li P and Alper H, Poly(ethylene glycol) promoted reactions of vinylic dibromides. Dehydrohalogenation and palladium(0)-catalyzed formal oxidative homologation. *J Org Chem* **51**:4354–4356 (1986).
- Cao YQ, Chen BH and Pei BG, Cyanidation of halogen compounds and esters catalyzed by PEG400 without solvent. *Synth Commun* **31**:2202–2206 (2001).
- Du YF, Cao YQ, Dai Z and Chen BH, A Study on the heterogeneous reaction of trialkylsilyl chlorides with inorganic salts and monocarboxylates catalyzed by PEG400. *Journal of Chemical Research(S)* **3**:223–225 (2004).
- Cao YQ, Dai Z, Zhang R and Chen BH, A practical Knoevenagel condensation catalyzed by PEG400 and anhydrous K<sub>2</sub>CO<sub>3</sub> without solvent. *Synth Commun* **34**:2965–2971 (2004).
- Windholz M, *The Merck Index*, 10th edn, Merck & Co Inc, Rahway, NJ, USA (1983).
- Buckingham J, *Dictionary of Organic Compounds*, 5th edn, Chapman–Hall, New York (1982).
- Protiva M, Novak L and Sedivy Z, Antihistamine substances *p*-substituted *N*-( $\alpha$ -phenylethyl) ethylenediamine derivatives. *Collection Czech Chem Commun* **27**:2102–2110 (1962).