



## **NaBH<sub>4</sub>/NaNO<sub>3</sub>/H<sub>2</sub>O: A Convenient System for Selective Reduction of Aldehydes VS. Ketones to their Corresponding Alcohols**

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### **ABSTRACT**

NaBH<sub>4</sub> (1.25 equivalents) & NaNO<sub>3</sub> (3 equivalents) reduce a variety of aldehydes in the presence of ketones to their corresponding alcohols. Also, regioselectivity and exclusive 1,2-reduction enals to their corresponding allylic alcohols in high to excellent yields was achieved successfully with this reducing system. The reduction reactions were carried out in water as green solvent in high to excellent yields of the products. A nitrate-borane complex [H<sub>3</sub>B-NO<sub>3</sub>]Na is possibly the active reductant in the reaction mixture.

**Key words:** NaBH<sub>4</sub>, Selective Reduction, Aldehydes, NaNO<sub>3</sub>.

### **INTRODUCTION**

The chemoselective reduction of aldehydes without affecting ketones is a well-known strategy in organic synthesis. This subject is of great interest <sup>1</sup> and numerous reducing systems and modified hydroborates have been reported for this subject <sup>2-4</sup> such as by use of low temperatures <sup>5-6</sup> addition of thiols <sup>7</sup>, metal salts <sup>8</sup>, resins <sup>9</sup> and polyethylene glycol <sup>10</sup> or by several modified borohydrides <sup>11-13</sup>. We decided to investigate the reducing properties of NaBH<sub>4</sub> in the presence of NaNO<sub>3</sub> as the co-reagent for the reduction of aldehydes vs. ketones to their corresponding

alcohols. Herein, we wish to report a convenient method for the reduction of aldehydes vs. ketones to their corresponding primary alcohols with NaBH<sub>4</sub>/NaNO<sub>3</sub> as reducing system in water.

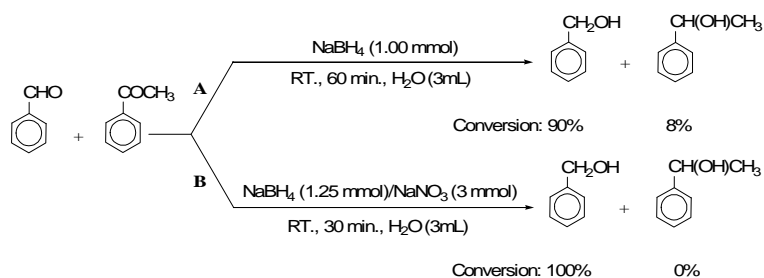
### **RESULTS AND DISCUSSION**

Ketones are less reactive than aldehydes in reduction reactions. But this character is not sufficient for selectively reduction of aldehydes vs. ketones (scheme 1, Path A). To achieve for more selectivity, the reduction reactions can be done slower. For this purpose we have examined the reduction reaction of benzaldehyde as model

compound with  $\text{NaBH}_4$  in aqueous media in the presence and absence of  $\text{NaNO}_3$  as shown in scheme 1. Our observation showed that the reduction reaction of 1 eq. benzaldehyde completed at room temperature in the presence of 3 eq.  $\text{NaNO}_3$  and 1.25 eq.  $\text{NaBH}_4$  as shown in table 1.

For investigate of selectively reduction reaction, a mixture of benzaldehyde (1 eq.) and acetophenone (1 eq.) was prepared. The reaction

mixture was treated with 1.25 equivalents of  $\text{NaBH}_4$  and 3 equivalents of  $\text{NaNO}_3$  in 3 mL water at room temperature. As shown in scheme 1, after 30 min, we have observed that the reduction of benzaldehyde to benzyl alcohols was complete but acetophenone was intact material *i.e.* the competition for reduction was favor of benzaldehyde (scheme 1, path B). This result can not achieve by only using  $\text{NaBH}_4$  (scheme 1, path A).

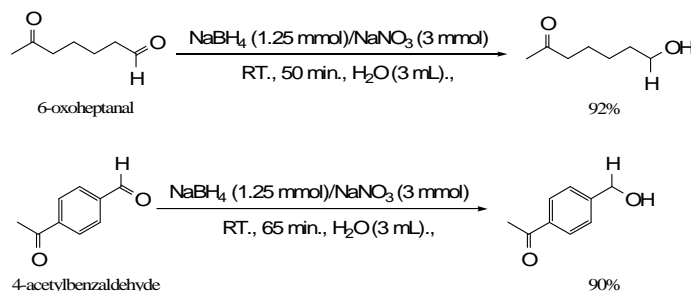


**Scheme 1:**

The efficiency of this protocol was examined by the reduction of a variety of aldehydes in the presence of acetophenone. All reductions were completed within 30-180 min as shown in table 2. The molar ratio of  $\text{NaBH}_4$  is not different according to the nature of the substrates. 1.25 molar equivalents of  $\text{NaBH}_4$  and 3 molar equivalents of  $\text{NaNO}_3$  per one equivalents of the substrate were sufficient to complete conversion of aldehydes to

the corresponding alcohols in excellent yields (90-95%).

For more investigate, the reduction of 6-oxoheptanal and 4-acetylbenzaldehyde as ketoaldehydes to their corresponding ketoalcohols has been done as shown in scheme 2. The reductions were completed within 50-65 min and the corresponding ketoalcohols have been isolated in excellent yields (90-92%).



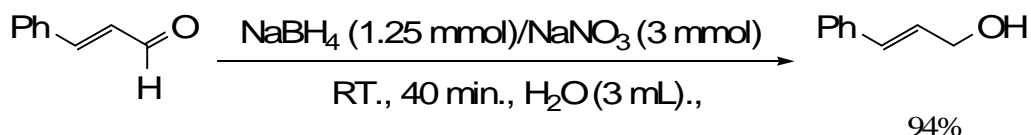
**Scheme 2:**

The preparation of ally alcohols from the reduction of conjugated carbonyl compounds is conventional in organic synthesis. Regioselective 1,2-reduction of  $\alpha,\beta$ -unsaturated aldehydes due to

competing 1,2- vs. 1,4-attack by the hydride is often difficult to achieve in organic synthesis. The tendency of sodium borohydride to reduce enals in a conjugate sense is highly dependent on solvent

and often ignored.<sup>14</sup> However, several specific reagents are available.<sup>15</sup> In this context, we also investigated the possibility of the 1,2-reduction of  $\alpha,\beta$ -unsaturated aldehydes and ketones with  $\text{NaBH}_4/\text{NaNO}_3/\text{H}_2\text{O}$  system. The reduction of cinnamaldehyde by 1.25 molar equivalents of  $\text{NaBH}_4$  in the presence of 3 molar equivalents of

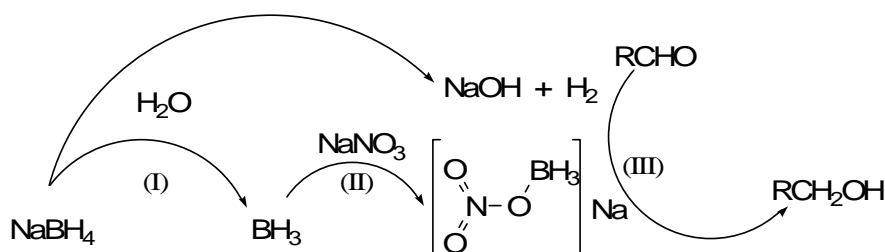
$\text{NaNO}_3$  was thus carried out exclusively in 1,2-reduction manner within 40 minutes at room temperature. In this reaction, cinnamyl alcohol was obtained in 94% yield as shown in scheme 3 (Table 2, entry 9). Citral also showed the best efficiency and regioselectivity under this protocol (Table 2, entry 10).



Scheme 3:

The mechanism for the influence of  $\text{NaNO}_3$  is not clear, but as shown in scheme 4 we think that a possible derivative of nitrate-borane as active reductant may form *in situ* under reaction condition. The possibility to form borane complex via nucleophilic attack is also well-known<sup>16-17</sup>. The

nitrate-borane specie is generated by the nucleophilic attack of nitrate ion on borane (scheme 4, II) formed from sodium borohydride and water (scheme 4, I). The nitrate-borate is less reactive than  $\text{NaBH}_4$  and diminishes reactivity.



Scheme 4:

## EXPERIMENTAL

### General

All substrates and reagents were purchased from commercially sources with the best

quality. IR and  $^1\text{H}$  NMR spectra were recorded on PerkinElmer FT-IR RXI and 300 MHz Bruker spectrometers, respectively. The products were characterized by their  $^1\text{H}$  NMR or IR spectra and comparison with authentic samples (melting or

Table 1: The optimization reaction condition for the reduction of benzaldehyde (1 mmol) to benzyl alcohol in water (3 mL) at room temperature

Entry	$\text{NaBH}_4$ (mmol)	$\text{NaNO}_3$ (mmol)	Time (min)	Conversion (%) <sup>a</sup>
1	1	0	60	90
2	1	1	50	95
3	1	2	40	100
4	1	3	40	100
5	1.25	3	30	100
6	1.25	2	50	100
7	1.5	3	25	100

<sup>a</sup> Conversion monitored by TLC and refer to isolated pure product.

boiling points). Organic layers were dried over anhydrous sodium sulfate. All yields referred to isolated pure products. The purity of products was determinate by  $^1\text{H}$  NMR. Also, reactions are monitoring over silica gel 60  $\text{F}_{254}$  aluminum sheet. A typical procedure

In a round-bottomed flask (10 mL) equipped with a magnetic stirrer, a solution of  $\text{NaBH}_4$  (0.047 g, 1.25 mmol) and  $\text{NaNO}_3$  (0.255 g, 3 mmol)

in water (3 mL) was treated with 6-oxoheptanal (0.128 g, 1 mmol) in one portion. The mixture was stirred at room temperature for 50 minutes. Completion of the reaction was monitored by TLC (Hexane/EtOAc: 9/1). Then, water (5 mL) was added to the reaction mixture. The mixture was extracted with ether (3x10 mL) and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . Evaporation of the solvent afforded the pure 7-hydroxyheptan-2-one (0.236 g, 92%, Table 1, entry 7).

**Table 2: The Reduction of Aldehydes (1 mmol) vs. Acetophenone (1 mmol) by  $\text{NaBH}_4$  (1.25 eq.)/ $\text{NaNO}_3$  (3 mmol) in Water (3 mL) at Room Temperature**

Entry	Aldehydes	Products	Time/min	Yield <sup>a</sup> %
1	benzaldehyde	benzyl alcohol	30	93
2	4-bromobenzaldehyde	4-bromobenzyl alcohol	30	91
3	4-methylbenzaldehyde	4-methylbenzyl alcohol	60	90
4	4-nitrobenzaldehyde	4-nitrobenzyl alcohol	30	93
5	2-methoxybenzaldehyde	2-methylbenzyl alcohol	60	93
6	4-methoxybenzaldehyde	4-methoxybenzyl alcohol	180	95
7	6-oxoheptanal	7-hydroxyheptan-2-one	50	92
8	4-acetylbenzaldehyde	1-(4-(hydroxymethyl)phenyl)ethanone	65	90
9	cinnamaldehyde	cinnamyl alcohol	40	94
10	citral	3,7--dimethylocta-2,6-dien-1-ol	60	93

<sup>a</sup> Yields refer to isolated pure products

### CONCLUSION

In conclusion, we have shown that  $\text{NaBH}_4/\text{NaNO}_3/\text{H}_2\text{O}$  reduces a variety of aldehydes vs. ketones to their corresponding primary alcohols in high to excellent yields at room temperature. Reduction reactions were carried out with 1.25 molar equivalents of  $\text{NaBH}_4$  in the presence of 3 molar equivalents of  $\text{NaNO}_3$  in water as green solvent. In addition, regioselectivity of this system was also investigated with exclusive 1,2-reduction of conjugated enals to their corresponding allylic alcohols in excellent yields. All reductions were

accomplished with high efficiency of the reductions, using the appropriate molar ratios of  $\text{NaBH}_4$  and  $\text{NaNO}_3$ , convenient reaction times (30-180 min) and easy work-up procedure. Therefore this new protocol for chemoselective & regioselective reduction of aldehydes could be a useful addition to the present methodologies.

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