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Ultrasonic-Promoted Selective Reduction of Aldehydes *vs.* ketones by $NaBH_4/PhCO_2Na/H_2O$

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ABSTRACT

In this study, we have investigated the selective reduction of aldehydes *vs.* ketones by $NaBH_4/PhCO_2Na/H_2O$ system under ultrasound irradiation. $NaBH_4$ (1.25 equivalents) and $PhCO_2Na$ (2 equivalents) is optimized conditions for reduce a variety of aldehydes (1 mmol) in the presence of ketones (1 mmol) to their corresponding alcohols in water as green solvent in high to excellent yields of the product (90-95%). A benzoate-borane complex $[PhCO_2\text{-}H_3B]Na$ is possibly the active reductant in the reaction mixture.

Keywords: $NaBH_4$, Selective Reduction, Aldehydes, $PhCO_2Na$, Ultrasound.

INTRODUCTION

Ultrasound irradiation is an exciting new unconventional energy in organic synthesis during the past decade. The promoted organic reaction by ultrasound irradiation has higher yield, shorter reaction time and milder conditions[1].

The Reduction of aldehydes *vs.* ketones is interesting in organic synthesis[2]. For this achievement several modified borohydrides[2-3] have been reported. Also some reducing systems have been used for this purpose such as: use of low temperatures[4-5] addition of thiols[6], metal salts[7], resins[8] and polyethylene glycol [9]. In this context we have investigated the reducing properties of sodium borohydride ($NaBH_4$) in the presence of sodium benzoate ($PhCO_2Na$) as co-reagent for the reduction of aldehydes *vs.* ketones to their corresponding alcohols in water. This reducing system has been promoted by ultrasound irradiation.

RESULTS AND DISCUSSION

Aldehydes are more reactive than ketones in reduction reactions. But to achieve for more selectivity, the reduction reactions can be done slower. We have examined the reduction reaction of benzaldehyde as model compound with $NaBH_4$ in aqueous media in the presence and absence of $PhCO_2Na$. Our experiments showed that the reduction reaction of 1 eq. benzaldehyde completed

at room temperature in the presence of 2 eq. $PhCO_2Na$ and 1.25 eq. $NaBH_4$ in H_2O (3 mL) under ultrasonic irradiation (table 1,entry 10) as shown in scheme 1.

After this achievement, we have decided to investigate of chemoselective reduction of aldehydes *vs.* ketones under optimized reaction condition. So, a mixture of benzaldehyde (1 eq.) and acetophenone (1 eq.) was prepared. The reaction mixture was treated with 1.25 equivalents of $NaBH_4$ and 2 equivalents of $PhCO_2Na$ in 3 mL water at room temperature, as shown in scheme 2. After 60 min, we have observed that the reduction of benzaldehye to benzylalcohols was completed but acetophene was intact material, *i.e.* the competition for reduction was favor of benzaldehyde.

The efficiency of this protocol was examined by the reduction of a variety of aromatic aldehydes (Table 2, entry 1-11) and aliphatic aldehydes (Table 2, entry 14-15) in the presence of structurally different ketones (aliphatic and aromatic). All reductions were completed within 20-100 min as shown in table 2. 1.25 molar equivalents of $NaBH_4$ and 2 molar equivalents of $PhCO_2Na$ per one equivalents of the aldehyde were sufficient to complete conversion of aldehydes to the corresponding alcohols in excellent yields (90-95%).

Also, We have investigated the possibility of the 1,2-reduction of α,β-unsaturated aldehydes (Table 2, entry 12-13) in presence of α,β-unsaturated ketones with $NaBH_4/PhCO_2Na/H_2O$/U.S. system. The reduction of cinnamaldehyde and citral by 1.25 molar equivalents of $NaBH_4$ in the presence of 2 molar equivalents of $PhCO_2Na$ carried out exclusively in 1,2-reduction manner within 60-40 minutes at room temperature. In this reaction, the corresponding α,β-unsaturated alcohol were obtained in 90% yield as shown in scheme 3. Cinnamaldehyde and Citral have showed the best efficiency and regioselectivity under this protocol.

The mechanism for the influence of $PhCO_2Na$ is not clear, but as shown in scheme 4, we think that a possible derivative of benzoate-borane as an active reductant may form *in situ* under reaction conditions. The benzoate-borane specie is generated by the nucleophilic attack of benzoate ion on borane (scheme 4, II) that formed from sodium borohydride in water (scheme 4, I). The benzoate-borate is less reactive than $NaBH_4$ and diminishes reactivity.

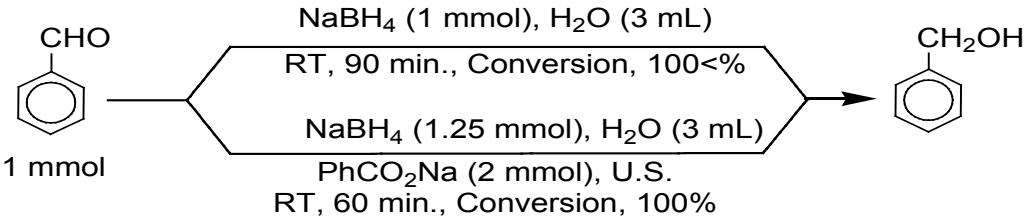
EXPERIMENTAL

General

All substrates and reagents were purchased from commercially sources with the best quality. IR and ^1H NMR spectra were recorded on PerkinElmer FT-IR RXI and 300 MHz Bruker spectrometers, respectively. The products were characterized by their ^1H NMR or IR spectra and comparison with authentic samples (melting or boiling points). Organic layers were dried over anhydrous sodium sulfate. All yields referred to isolated pure products. The purity of products was determinate by ^1H NMR. Also, reactions are monitoring over silica gel 60 F_{254} aluminum sheet. Sonication was carried out using a Cole Palmer high intensity ultrasonic processor (600W, 20 KHz) via a micro-tip probe and 50% amplitude.

A typical Procedure for Reduction of aldehydes with $NaBH_4/PhCO_2Na/H_2O$/U.S. system

In a round-bottomed flask (10 mL) equipped with a magnetic stirrer, a solution of $NaBH_4$ (0.047 g, 1.25 mmol) and $PhCO_2Na$ (0.138 g, 2 mmol) in water (3 mL) was treated with benzaldehyde

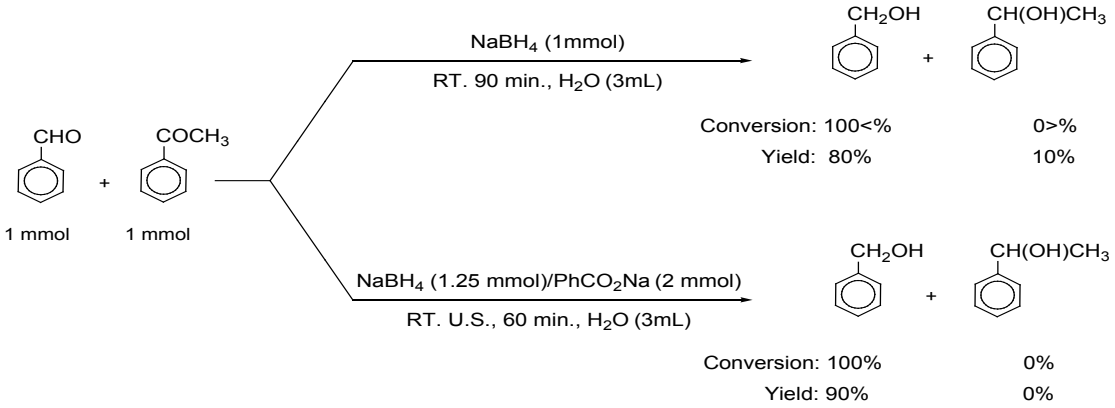


Scheme 1

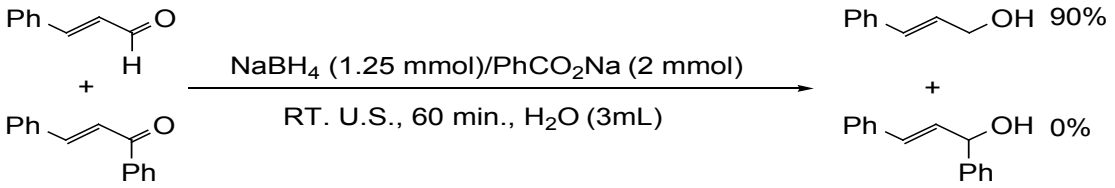
(0.106 g, 1 mmol) in one portion. The mixture was stirred and irradiated with ultrasound waves at room temperature for 60 minutes. Completion of the reaction was monitored by TLC (Hexane/EtOAc: 9/1). Then, water (5 mL) was added to the reaction mixture. The mixture was extracted with ether (3×10 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent afforded the pure benzyl alcohol (0.097 g, 90%).

A typical Procedure for Competitive Reduction of aldehydes and ketones with $NaBH_4$/$PhCO_2Na$/H_2O/U.S. system

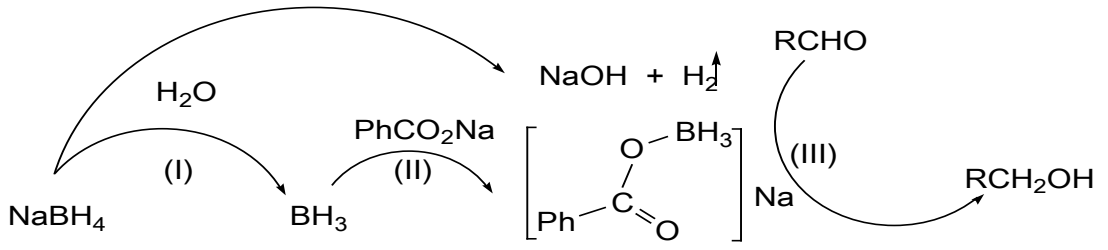
In a round-bottomed flask (10 ml) equipped with a magnetic stirrer, a solution of benzaldehyde (0.106 g, l mmol) and acetophenone (0.120 g, 1 mmol) in H_2O (3 mL) was prepared. To this solution, $NaBH_4$ (0.047 g, 1.25 mmol) and $PhCO_2Na$ (0.138 g, 2 mmol) was added. The mixture was stirred and



Scheme 2



Scheme 3



Scheme 4

Table 1: The optimization reaction condition for the reduction of benzaldehyde (1 mmol) to benzylalcohol in water (3 mL) at room temperature and under ultrasonic irradiation

Entry	$NaBH_4$ (mmol)	$PhCO_2Na$ (mmol)	Time (min)	Condition	Conversion (%)[a]
1	1	0	90	RT	100<
2	1	1	90	RT	100<
3	1	2	90	RT	100<
4	1.5	2	90	RT	100<
5	2	2	90	RT	100<
6	2	3	90	RT	100<
7[b]	1	1	90	RT/U.S.	100<
8[b]	1	2	90	RT/U.S.	100
9	0.5	2	90	RT/U.S.	100<
10	1.25	2	60	RT/U.S.	100
11	1.5	2	50	RT/U.S.	100
12	1.25	3	50	RT/U.S.	100

[a] Conversion monitored by TLC and refer to isolated pure product. [b] Sonication was carried out using a Cole Palmer high intensity ultrasonic processor (600W, 20 KHz) *via* a micro-tip probe and 50% amplitude.

Table 2: The Reduction of Aldehydes (1 eq.) *vs.* Ketones (1 eq.) by $NaBH_4$ (1.25 eq.)/$PhCO_2Na$ (2 mmol) in Water (3 mL) at Room Temperature under ultrasonic irradiation.[a]

Entry	Aldehydes	Ketones[b]	Time/min.[c]	Yield[d]/%
1	benzaldehyde	Acetophenone	60	92
2	benzaldehyde	benzophenone	60	90
3	benzaldehyde	4-phenycyclohexanone	60	95
4	4-bromobenzaldehyde	Acetophenone	60	90
5	3-methylbenzaldehyde	benzophenone	80	91
6	4-nitrobenzaldehyde	4-phenycyclohexanone	40	90
7	4-bromobenzaldehyde	benzophenone	60	90
8	4-methylbenzaldehyde	4-phenycyclohexanone	90	93
9	3-methoxylbenzaldehyde	Acetophenone	85	95
10	2-methoxylbenzaldehyde	benzophenone	100	90
11	4-methoxybenzaldehyde	4-phenycyclohexanone	90	95
12	cinnamaldehyde	chalcone	40	90
13	citral	chalcone	30	90
14	butanal	2-pantanone	20	94
15	hexanal	4-phenycyclohexanone	20	92

[a] Sonication was carried out using a Cole Palmer high intensity ultrasonic processor (600W, 20 KHz) *via* a micro-tip probe and 50% amplitude. [b] The reduction of ketones *vs.* aldehydes was 0%. [c] The reaction times refer to complete reduction of aldehydes to their corresponding alcohols. [d] Yields refer to isolated pure alcohols obtained from reduction of aldehydes.

irradiated with ultrasound waves at room temperature for 60 minutes. TLC monitored the progress of reaction. After 60 min, the reaction mixture was quenched by addition of distilled water (5 ml) and this mixture was then stirred for an additional 1 min. The mixture was extracted with CH_2Cl_2 (5×10 ml) and dried over anhydrous sodium sulfate.

Evaporation of the solvent and short column chromatography of the resulting crude material over silicagel by eluent of Hexane/EtOAc: 9/1 affords the pure liquid benzyl alcohol (0.099 g, 92%) as a sole product of reduction and acetophenone as an intact material (table 2, entry 1).

CONCLUSION

In this context, we have been shown that $NaBH_4/PhCO_2Na/H_2O$/U.S reduces a variety of aldehydes *vs.* ketones to their corresponding alcohols in high to excellent yields at room temperature. Reduction reactions were carried out with 1.25 molar equivalents of $NaBH_4$ in the presence of 2 molar equivalents of $PhCO_2Na$ 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 $NaBH_4$ and $PhCO_2Na$, convenient reaction times (20-100 min) under green chemistry protocol, and easy work-up procedure.

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