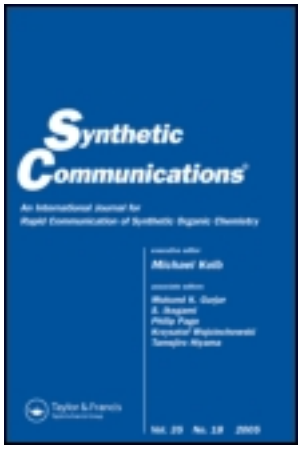

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Rapid Aqueous Borohydride Reduction of Carbonyls Under Sealed-Tube Microwave Conditions

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Accepted author version posted online: 27 Oct 2011.Published online: 26 Mar 2012.

To cite this article: S. Shaun Murphree , Jeremy D. Mason , Theodore G. Bean & Michelle C. Perry (2012): Rapid Aqueous Borohydride Reduction of Carbonyls Under Sealed-Tube Microwave Conditions, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 42:13, 1979-1986

To link to this article: http://dx.doi.org/10.1080/00397911.2010.551171

Synthetic Communications®, 42: 1979–1986, 2012

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2010.551171

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RAPID AQUEOUS BOROHYDRIDE REDUCTION OF CARBONYLS UNDER SEALED-TUBE MICROWAVE CONDITIONS

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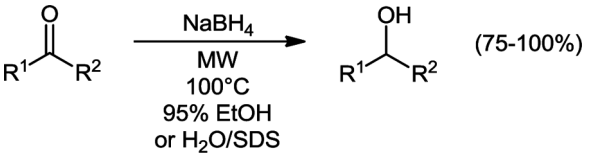
GRAPHICAL ABSTRACT



Abstract *Ketones and aldehydes are conveniently and rapidly reduced to the corresponding alcohols in good yields using sodium borohydride under sealed-tube microwave conditions in either 95% ethanol or water. In purely aqueous systems, highly aliphatic substrates are sluggish, but this can be overcome by introducing sodium dodecyl sulfate (SDS) at the critical micelle concentration. With a 2:1 substrate/borohydride ratio and a reaction temperature of 100 °C, reduction is typically complete within 1 min in 95% ethanol and 5 min in water/SDS. The methodology is well suited for parallel and combinatorial synthetic approaches.*

Keywords Aldehydes; aqueous; ketones; microwave; sodium borohydride

INTRODUCTION

The discovery of synthetic methodology conforming to green principles continues to be the subject of intense investigation.[1] Two innovations have shown particular promise in this regard. First, microwave-assisted organic synthesis (MAOS) allows for rapid access to target compounds, often in greater yield and with fewer by-products.[2] Second, the emerging use of water as a solvent for organic reactions promises both to reduce the environmental burden of waste solvent and to mitigate the energy consumption associated with solvent recovery.[3] It has become increasingly evident that these two innovations can be used to considerable synthetic advantage.[4] With this backdrop, the current study examines the scope and limitations of aqueous microwave conditions for the microwave-mediated aqueous borohydride reduction of carbonyl compounds.

Received December 21, 2010.

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The microwave-assisted reduction of carbonyls using aqueous borohydride has been previously reported; however, the reactions were carried out in open-vessel conditions using a modified domestic microwave oven.[5] To extend this methodology for use in industry-standard instrumentation, it was thus necessary to explore the scope of this protocol under sealed-tube conditions using dedicated synthetic reactors with precise temperature control.

Sodium borohydride is thermally unstable in aqueous and alcoholic solutions;[6] therefore, it seemed prudent first to examine the behavior of the reducing agent in various solvent systems in order to define an acceptable reaction temperature range that avoids the maximum operating pressure of 20 bar. In 95% ethanol, pressures remained comfortably below the limit at temperatures as high as 120 °C (Fig. 1). Introducing more water into the system accelerated the generation of hydrogen; however, the pressure was still manageable even in pure water at 100 °C (Fig. 2). Clearly, the pressure is dependent upon other experimental parameters. In this case, 1.5 mmol of sodium borohydride was dissolved in a total volume of 5.0 mL (the maximum recommended fill volume, leaving a headspace of 5.0 mL). Thus, the pressure attained in pure water (10 bar) roughly corresponds to the hydrogen generated from the hydrolysis of the first equivalent of hydride.

To examine the impact of the solvent on chemical conversion, acetophenone was used as a test substrate (Fig. 3). In 95% ethanol at 100 °C, quantitative conversion was achieved within 30 s. The reduction was somewhat more sluggish in water, requiring 5 min for 97% conversion, but the results were still very promising. These conditions were then applied to a series of aldehydes and ketones to explore the scope and limitations of the method (Scheme 1, Fig. 4, and Table 1).

Virtually all substrates provided excellent yields of the corresponding alcohols in 95% ethanol. The sole exception was camphor (entry 7), which tended to sublime

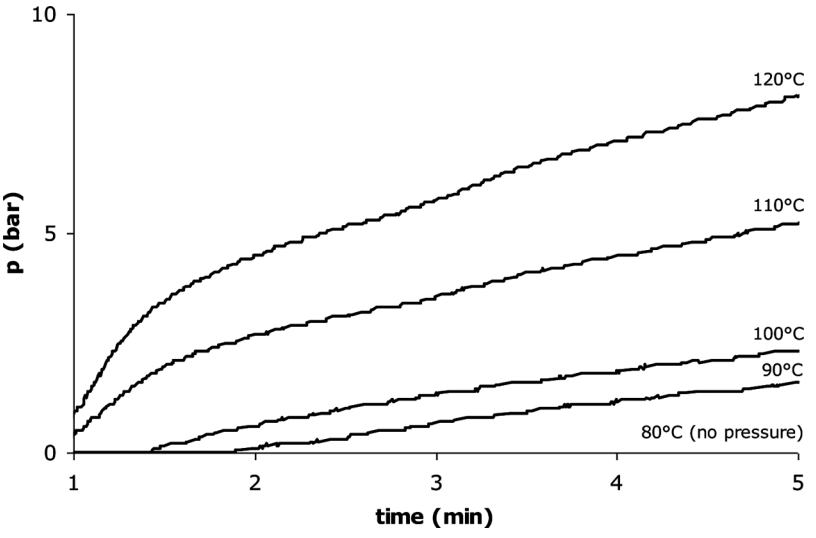


Figure 1. Pressure generation of sodium borohydride in 95% ethanol. Conditions: 0.30 M sodium borohydride in 95% ethanol with total fill volume of 5.0 mL.

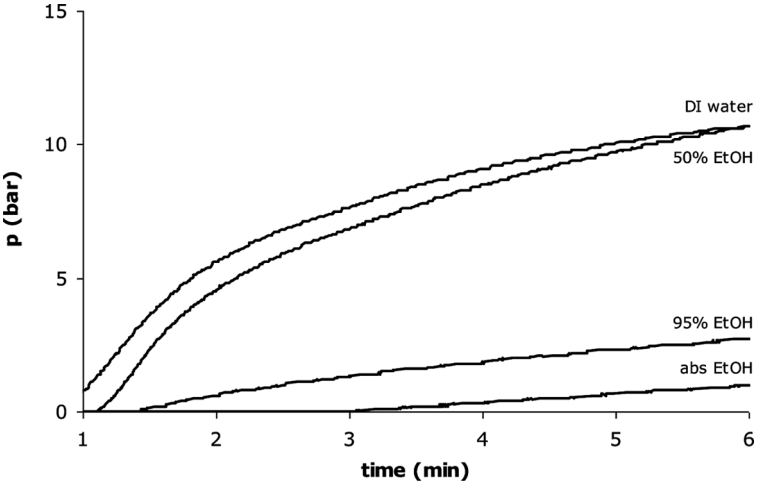


Figure 2. Pressure generation of sodium borohydride in aqueous ethanol systems. Conditions: 0.30 M sodium borohydride with total fill volume of 5.0 mL at 100 °C.

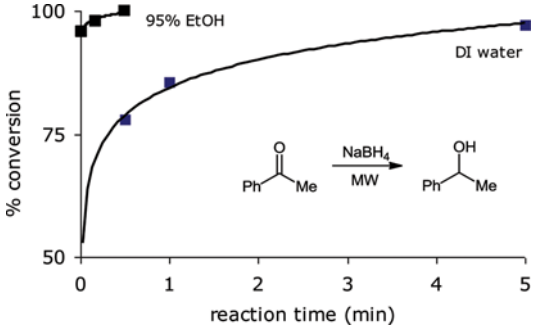


Figure 3. Reduction of acetophenone in ethanol and water. Conditions: 3.0 mmol acetophenone; 1.5 mmol $NaBH_4$, 5.0 mL fill volume, 100 °C. (Figure is provided in color online.)

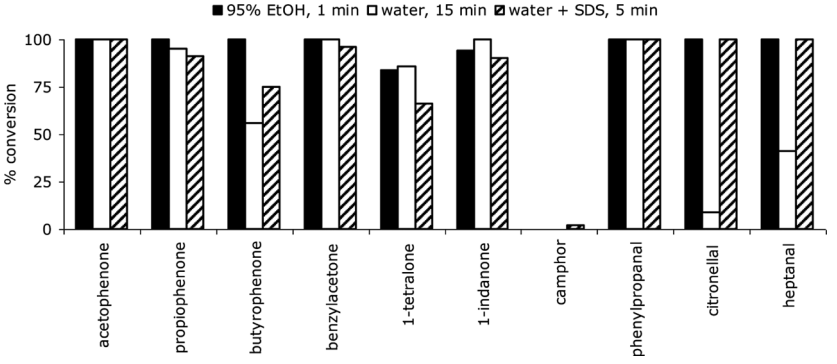
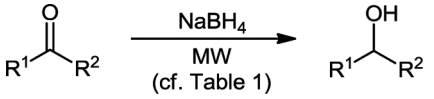
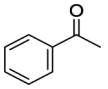
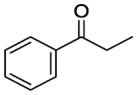
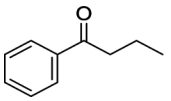
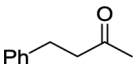
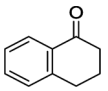
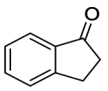
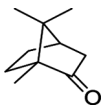
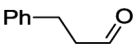
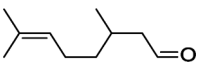
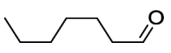


Figure 4. Product yields.



Scheme 1. Microwave-mediated borohydride reduction of ketones and aldehydes.

Table 1. Microwave-mediated borohydride reductions of ketones and aldehydes[a]

Entry	Substrate	Conversion % @ 100 °C			Aqueous solubility (mM)[b]
		95% EtOH (1 min)	Water (15 min)	8.1 mM SDS (5 min)	
1		100	100	100	20
2		100	95	91	8.1
3		100	56	75	3.4
4		100	100	96	13
5		84[c]	86[d]	66	3.4
6		94[e]	100	90	4.6
7		5[f]	0	2	6.9
8		100	100	100	9.9
9		100	9	100	2.9
10		100	41	100	13

[a]Molar ratios of substrate/borohydride are 2:1 for 95% ethanol and 3:2 for aqueous systems.
[b]Calculated using ACD/Labs Software v11.02 via SciFinder.
[c]94% after 5 min.
[d]94% after 30 min.
[e]98% after 5 min.
[f]92% after 5 min in tetrahydrofuran.

under microwave irradiation and condense along the top of the vial (this phenomenon can be suppressed by using tetrahydrofuran, in which camphor is soluble). Changing the solvent to pure water led to much more uneven results. While the smaller ketones and aldehydes still provided alcohols in excellent yield (albeit with longer reaction times), the highly aliphatic substrates, such as citronellal and heptaldehyde (entries 9 and 10), were oddly recalcitrant.

The use of surfactants in aqueous systems involving sparingly soluble organic components is well documented,[7] so it was reasoned that such an approach might prove advantageous for these sluggish examples. Indeed, adding sodium dodecyl sulfate (SDS) at the critical micelle concentration (CMC) had the desired effect. All reactions were accelerated, allowing for a reaction time of only 5 min across the board. Moreover, the yields for the aliphatic aldehydes were brought in line with the other substrates.

The nature of this effect is somewhat curious. As Table 1 demonstrates, the yields in water do not correlate well with the aqueous solubilities of the starting materials. One reasonable explanation for the anomalous behavior of citronellal and heptanal is that hydrophobic interactions induce a globular conformation, which obscures the electrophilic center. Thus, the surfactant may simply serve to stabilize the extended conformers of the aldehydes, as opposed to frank micellar catalysis.

In summary, aldehydes and ketones are cleanly and rapidly reduced using aqueous sodium borohydride under sealed-tube microwave conditions in good to excellent yields. As the aliphatic nature of the substrate increases, the facility of reaction decreases in pure water. However, the addition of SDS at the CMC can compensate for this effect. The present methodology should prove particularly useful for parallel and combinatorial synthesis.

EXPERIMENTAL

All reactions were carried out under sealed-tube conditions in a Biotage Initiator microwave reactor with the following settings: prestir = 5 s; absorbance level = high; fixed hold time = on. Sodium borohydride was obtained from Acros Organics (New Jersey, USA); all other chemicals were purchased from Sigma-Aldrich (Missouri, USA). Materials were used without further purification.

3-Phenylpropanol (Method A)

Sodium borohydride (56.7 mg, 1.5 mmol), 95% ethanol (4.6 mL), and 3-phenylpropionaldehyde (395 mL, 3.0 mmol) were charged to a 10-mL microwave vial equipped with a magnetic stir bar. The vial was capped and heated in the microwave reactor for 1 min at 100 °C. After cooling to 40 °C, the vial was opened and the contents were transferred to a separatory funnel containing deionized water (ca. 100 mL) and extracted with dichloromethane (2×25 mL). The organic extracts were combined, dried over sodium sulfate, and concentrated in vacuo to give 3-phenylpropanol as a clear oil in quantitative yield.

3-Phenylpropanol (Method B)

Sodium borohydride (56.7 mg, 1.5 mmol), deionized water (4.0 mL), and 3-phenylpropionaldehyde (395 mL, 3.0 mmol) were charged to a 10-mL microwave vial equipped with a magnetic stir bar. The vial was capped and heated in the microwave reactor for 15 min at 100 °C. After cooling to 40 °C, the vial was opened and the contents were transferred to a separatory funnel containing deionized water (ca. 100 mL) and extracted with dichloromethane (2 × 25 mL). The organic extracts were combined, dried over sodium sulfate, and concentrated in vacuo to give 3-phenylpropanol as a clear oil in quantitative yield.

Preparation of 0.67 M Aqueous Sodium Borohydride Solution with 8.2 mM SDS

Sodium dodecyl sulfate (117 mg, 0.41 mmol), sodium borohydride (1,261 g, 33.3 mmol), and deionized water (30 mL) were charged to a 50-mL beaker. After carefully stirring with a spatula to dissolve the solids, the solution was transferred to a 50-mL volumetric flask and diluted to the mark with deionized water. The final solution was stored at 5 °C and used within 12 h.

3-Phenylpropanol (Method C)

3-Phenylpropionaldehyde (395 mL, 3.0 mmol) and aqueous sodium borohydride/SDS solution (3.0 mL, 2.0 mmol) were charged to a 10-mL microwave vial equipped with a magnetic stir bar. The vial was capped and heated in the microwave reactor for 5 min at 100 °C. After cooling to 40 °C, the vial was opened, and the contents were transferred to a separatory funnel containing deionized water (ca. 100 mL) and extracted with dichloromethane (2 × 25 mL). The organic extracts were combined, dried over sodium sulfate, and concentrated in vacuo to give 3-phenylpropanol (405 mg, 99%) as a clear oil.

Spectral Data

1-Phenylpropanol (Entry 1)[8]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24–7.40 (m, 5H), 4.90 (q, $J = 6.34$ Hz, 1H), 1.73 (br s, 1H), 1.50 (d, $J = 6.59$ Hz, 3H).

1-Phenylpropan-1-ol (Entry 2)[9]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24–7.38 (m, 5H), 4.58 (t, $J = 6.78$ Hz, 1 Hz), 1.96 (br s, 1H), 1.68–1.88 (m, 2H), 0.91 (t, $J = 7.50$ Hz, 3H).

1-Phenylbutane-1-ol (Entry 3)[10]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23–7.37 (m, 5H), 4.67 (dd, $J = 5.86$, 5.79 Hz, 1H), 1.81 (br s, 1H), 1.74–1.84 (m, 2H), 1.63–1.72 (m, 2H), 0.93 (t, $J = 7.50$, 3H).

4-Phenylbutan-2-ol (Entry 4)[10]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15–7.32 (m, 5H), 3.83 (sext, $J = 6.22$ Hz, 1H), 2.62–2.82 (m, 2H), 1.70–1.85 (m, 2H), 1.58 (br s, 1H), 1.23 (d, $J = 5.86$, 3H).

α-Tetralol (Entry 5)[9]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06–7.46 (m, 4H), 4.78 (t, $J = 4.76$ Hz, 1H), 2.68–2.88 (m, 2H), 1.73–2.03 (m, 4H), 1.71 (br s, 1H).

1-Indanol (Entry 6)[11]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20–7.44 (m, 4H), 5.24 (t, $J = 6.04$ Hz, 1H), 3.06 (ddd, $J = 15.84$, 8.51, 4.76 Hz, 1H), 2.82 (app quint, $J = 7.78$ Hz, 1H), 2.43–2.54 (m, 1H), 1.89–1.99 (m, 1H), 1.79 (br s, 1H).

Isoborneol (Entry 7)[12]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.70 (t, $J = 6.25$ Hz, 1H), 1.70–1.80 (m, 6H), 1.64 (td, $J = 12.18$, 3.29 Hz, 1H), 1.25–1.40 (m, 1H), 0.91 (s, 3H), 0.87 (s, 3H), 0.79 (s, 3H).

3-Phenylpropan-1-ol (Entry 8)[13]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16–7.32 (m, 5H), 3.68 (t, $J = 6.40$ Hz, 2H), 2.71 (t, $J = 7.70$ Hz, 2H), 1.85–1.94 (m, 2H), 1.48 (br s, 1H).

Citronellol (Entry 9)[14]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.05–5.12 (m, 1H), 3.61–3.74 (m, 2H), 1.87–2.07 (m, 2H), 1.67 (d, $J = 1.10$ Hz, 3H), 1.59 (s, 3H), 1.50–1.70 (m, 2H), 1.27–1.43 (m, 3H), 1.11–1.25 (m, 1H), 0.90 (d, $J = 6.59$ Hz, 3H).

1-Heptanol (Entry 10)[15]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.63 (t, $J = 6.78$ Hz, 2H), 1.56 (t, $J = 6.96$ Hz, 2H), 1.46 (br s, 1H), 1.21–1.39 (m, 8H), 0.87 (t, $J = 6.96$ Hz, 3H).

ACKNOWLEDGMENTS

The authors gratefully acknowledge Allegheny College and the National Science Foundation (CCLI 0837640) for generous support of this project.

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