Simple and Efficient Microwave-Assisted Hydrogenation Reactions at Moderate Temperature and Pressure

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Abstract: A generally applicable method for the introduction of gaseous hydrogen into a sealed reaction system to perform hydrogenation reactions under microwave irradiation has been developed. Several different types of substrates are easily reduced in short reaction times with moderate temperatures between 80 °C and 100 °C with 50 psi of hydrogen. The use of simultaneous cooling is also applied to the hydrogenation of more difficult substrates.

Key words: hydrogenations, microwave, palladium, reductions, simultaneous cooling

Hydrogenation is one of the most powerful transformations in synthetic chemistry. An astounding number of natural product syntheses involve at least one hydrogenation step. These reactions often require long reaction times to affect complete conversion to product. In addition, hydrogenation reactions can also require harsh reaction conditions such as high pressures and/or temperatures.

Over the past 20 years, the area of microwave chemistry has become a powerful method for performing challenging reactions in shorter amounts of time with higher yields and purity.[1] As with several other types of metal-catalyzed reactions, hydrogenation reactions also benefit from the use of microwave irradiation to accelerate the reaction and improve yields. Unlike conventional hydrogenation methods that rely on gaseous hydrogen, reactions performed in a microwave typically require the addition of a reagent that will generate the hydrogen gas in situ or will transfer hydrogen directly to the substrate. Ammonium formate is the most common hydrogen donor used for microwave-assisted hydrogenation reactions.[2] The disadvantages of using ammonium formate in a sealed microwave reaction vessel are the development of high pressures due to the generation of carbon dioxide and the sublimation of the ammonium formate at elevated temperatures. In addition, an excess of the ammonium formate is typically necessary to drive the reaction to completion causing the need for additional purification. Other hydrogen donors that have been reported in microwave-assisted hydrogenations include solid-supported formates,[3] sodium formate,[4] isopropanol for ketone reductions,[5] and sodium borohydride for imine reductions.[6] While these microwave-assisted hydrogenation reactions give good yields of the reduced product, the additional hydrogen donor reagent typically increases the purification necessary for the reaction. Gaseous hydrogen is a more suitable hydrogen donor as it requires no additional purification step for its removal, but getting the hydrogen gas into the reaction vessel can be challenging. There are a few examples of dechlorination[7] reactions and hydrogenation reactions[8] performed in a microwave reactor that use hydrogen gas, but these methods are not generally applicable for introducing the gaseous reagent to the reaction vessel and for performing these reactions.

A simple system has been developed for the introduction of hydrogen gas into a sealed microwave reaction system. The set-up provides both fiber optic temperature control and pressure feedback control.[9] As a model reaction, the hydrogenation of *trans*,*trans*-1,4-diphenyl-1,3-butadiene was performed with the gaseous reagent addition system. Using the ideal gas law, the amount of hydrogen necessary for complete conversion to product is about 45 psi. Each of these reactions was performed by charging the reaction vessel to 50 psi to give only a slight excess of hydrogen gas resulting in minimal waste.

The hydrogenation of diene **1** was initially performed with palladium on carbon in ethanol, a standard catalyst and solvent system for hydrogenation reactions. When the reaction was performed at 80 °C, 78% conversion to product was obtained (Table 1). Increasing the temperature to 100 °C neither increased nor decreased the conversion of the reaction. Interestingly, a further increase in temperature to 120 °C saw a decrease in the conversion to 21%, and increasing the temperature even further to 150 °C resulted in almost no conversion to product. This unusual temperature trend was unexpected and is an area of continued research.

With the optimized temperature, different solvents were explored for the hydrogenation reaction. As previously discussed, when the reaction was performed in ethanol, 78% conversion was observed. Changing the solvent to ethyl acetate, another common solvent for hydrogenation reactions, improved the conversion to >99% (Table 2). The reaction was also performed with both tetrahydrofuran and dichloromethane, but low conversions were obtained. Toluene gave good conversion to product, but it also presented some distinct disadvantages to the other solvents. Toluene does not suspend the palladium on carbon as well as the other solvents, and as a result small

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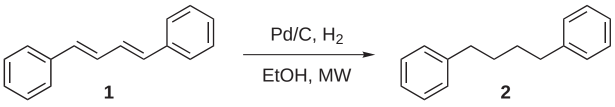
Table 1 Temperature Study[a]

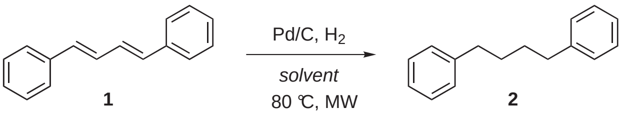


Temp (°C)	Conversion (%)[b]
80	78
100	78
120	21
150	2

[a] Conditions: **1** (0.5 mmol), Pd/C (10 mol%), H_2 (50 psi), EtOH (2 mL), 5 min.
[b] Determined by GC.

amounts of the catalyst can stick to the sides of the reaction vessel which can produce arcing in the microwave field.[10] This arcing will etch the glass vessel, and can result in vessel failure. Therefore, toluene is not recommended as a solvent for these hydrogenation reactions at high concentrations of catalyst loading.

Table 2 Solvent Screen[a]



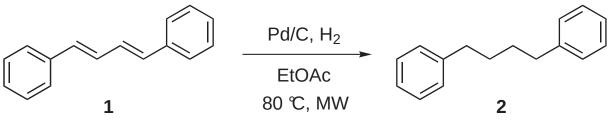
Solvent	Conversion (%)[b]
EtOH	78
EtOAc	>99
THF	6
Toluene	89
CH_2Cl_2	2

[a] Conditions: **1** (0.5 mmol), Pd/C (10 mol%), H_2 (50 psi), 80 °C, solvent (2 mL), 5 min.
[b] Determined by GC.

All of these initial studies were performed with high catalyst concentrations. To make this a more environmentally friendly and cost effective process, lower amounts of catalyst were explored for the hydrogenation of diene **1**. As shown in Table 3, catalyst concentrations as low as 1 mol% can be used with no detrimental effect to the conversions. This catalyst concentration study was limited by the small amounts of palladium on carbon required for the 1 mol% reaction, and even lower amounts of palladium catalyst can likely be used.

To ensure completeness of this microwave-assisted hydrogenation study, a direct comparison was made between the microwave method and conventional heating. This was achieved by performing the hydrogenation of diene **1** under reaction conditions, identical to those used in the microwave reactions, in a preheated oil bath. The exact same temperature, pressure, and time were used in the oil bath experiment [**1** (0.5 mmol), Pd/C (1 mol%), H_2 (50 psi), 80 °C, EtOAc (2 mL), 5 min hold], and careful control of the temperature profiles ensured accurate reproduction of the reaction conditions (Figure 1). The hydrogenation performed in the microwave resulted in complete conversion to product, while the reaction performed in the oil bath resulted in only 55% conversion. These results indicate that the microwave does indeed accelerate the reaction and has an influence on the outcome of the hydrogenation reaction.

Table 3 Catalyst Concentration Study[a]



Catalyst concentration (mol%)	Conversion (%)[b]
10	>99
5	>99
2	>99
1	>99

[a] Conditions: **1** (0.5 mmol), H_2 (50 psi), 80 °C, EtOAc (2 mL), 5 min.
[b] Determined by GC.

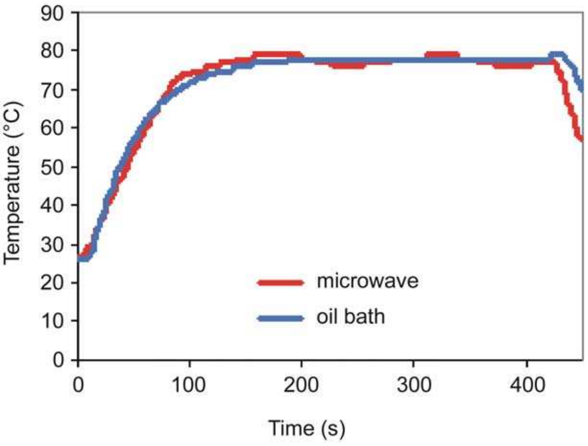
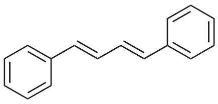
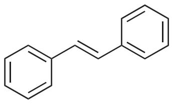
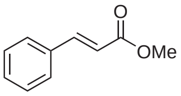
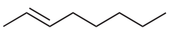
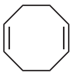
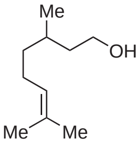
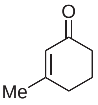
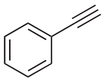
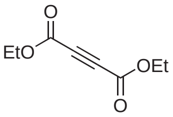
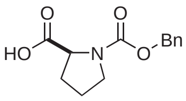
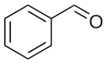
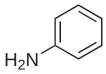


Figure 1 Temperature profiles for the hydrogenation of diene **1** in both the microwave and oil bath.

With the optimized conditions for the hydrogenation of diene **1**, the hydrogenation of various other unsaturated compounds was explored (Table 4). Conjugated alkenes **3** and **4** were each hydrogenated in three minutes to give better than 99% yield (entries 2 and 3). Non-conjugated alkenes (entries 4 and 5) can also be reduced in short reaction times to give excellent conversions.[11] Trisubstituted olefins can be hydrogenated in five minutes as well at 80 °C to give 99% yield (entry 6). α,β-Unsaturated ketone **8** required slightly harsher conditions to give the desired hydrogenated product, but none of the 1,2-reduced product was observed (entry 7). In addition to olefins, alkynes can be hydrogenated quickly and in high yield. Phenylacetylene (**9**) was hydrogenated to give ethylbenzene in >99% conversion while diethylacetylene dicarboxylate (**10**) gave >99% yield of the desired product (entries 8 and 9). A carbobenzyloxy protecting group was easily removed in five minutes to give the deprotected proline in excellent yield (entry 10). Lastly, a reductive amination between benzaldehyde and aniline gave 89% yield of the desired *N*-benzylaniline (entry 11).

Table 4 Hydrogenation of Various Substrates[a]

Entry	Substrate	Temp (°C)	Time (min)	Yield (%)[b]
1	 **1**	80	5	>99
2	 **3**	80	3	>99
3	 **4**	80	3	>99
4	 **5**	80	5	>99[c]
5	 **6**	80	10	>99[c]
6	 **7**	80	5	99
7	 **8**	100	20	89
8	 **9**	80	5	>99[c]
9	 **10**	80	3	>99
10	 **11**	80	5	>99
11	 **12a**  **12b**	80	3	98

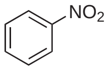
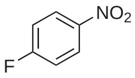
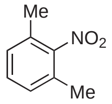
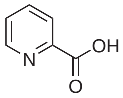
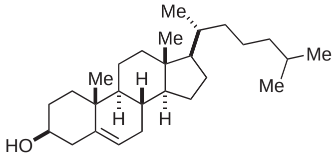
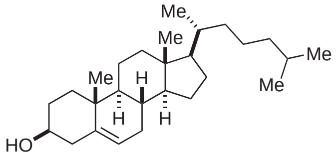
[a] Conditions: substrate (0.5 mmol), Pd/C (1 mol%), H_2 (50 psi), EtOAc (2 mL).
[b] Isolated yield.
[c] Conversion based on GC analysis.

Each of the reactions described above proceeded smoothly in as little as three minutes to give the desired products. Unfortunately, when the same reaction conditions were applied to the hydrogenation of nitrobenzene, only 70% yield could be obtained after 10 minutes at 80 °C. With these reaction conditions, only a small amount of power (<10 W) was required to maintain the temperature at 80 °C. To get more energy into the reaction mixture, the use of simultaneous cooling was explored.[12] When the same hydrogenation reaction of nitrobenzene was performed at 80 °C with simultaneous cooling, ca. 100 W of power was continuously added to the reaction mixture. This increase in the amount of power in the reaction resulted in complete conversion to product to give 85% isolated yield of the desired aniline (Table 5, entry 1).

Other nitrobenzene derivatives also benefited from the use of simultaneous cooling. 4-Fluoronitrobenzene (**14**) was hydrogenated using simultaneous cooling to give a high yield of the corresponding aniline derivative. The hydrogenation of hindered nitrobenzene **15** also proceeded in 15 minutes to give nearly quantitative yield of the desired aniline compound. The simultaneous cooling can also be used for the hydrogenation of pyridine derivatives as outlined in entry 4. The treatment of picolinic acid (**16**) with platinum oxide in the presence of hydrogen gas at 100 psi gave the desired pipecolic acid in excellent yield after only 10 minutes. Lastly, the hydrogenation of cholesterol (**17**) was explored. The reaction was performed at 80 °C with simultaneous cooling for 5 minutes to give high yield of the reduced product. When the exact same reaction was performed in the previously described preheated oil bath at 80 °C, only 3% isolated yield was obtained (entry 6). This clearly demonstrates that the rate enhancement for the hydrogenation of the cholesterol is not solely based on the temperature of the reaction mixture, and that the microwave is necessary to observe complete hydrogenation.

Several different examples have been presented that demonstrate the utility of microwave promoted hydrogenation reactions using a system designed for the use of gaseous hydrogen. Each of the reported examples proceeds in a short reaction time at moderate temperature and pressure (80–100 °C and 50–100 psi). The chemistry also can greatly benefit from the use of simultaneous cooling

Table 5 Hydrogenations with Simultaneous Cooling[a]

Entry	Substrate	Temp (°C)	Time (min)	Yield (%)[b]
1	 **13**	80	10	85
2	 **14**	80	15	>99
3	 **15**	80	15	>99
4	 **16**	80	10	>99[c]
5	 **17**	80	5	>99
6	 **17**	80	5	3[d]

[a] Conditions: substrate (0.5 mmol), Pd/C (1 mol%), H_2 (50 psi), EtOAc (2 mL), simultaneous cooling.

[b] Isolated yield.

[c] Conditions: **16** (0.5 mmol), PtO_2 (10 mol%), H_2 (100 psi), EtOH (2 mL).

[d] Performed in an oil bath at 80 °C.

in reactions that require higher power levels to achieve complete hydrogenation. Work is in progress to apply this system to other functional group hydrogenations as well as to extend the method to more complex hydrogenation reactions.

Acknowledgment

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References and Notes

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(9) **Experimental Set-up.**
All reactions were performed with a CEM Discover single mode microwave reactor equipped with a 300 W power source. A 10 mL fiber optic accessory was equipped with a gas inlet to allow introduction of hydrogen gas to the reaction vessel, and each of the reactions was performed in a CEM 10 mL microwave reaction vial. All temperature measurements were performed with a fiber optic probe, and 2 mL of solvent was used for each reaction to ensure ample submersion of the fiber optic probe.
General Procedure.
To a solution of *trans*,*trans*-1,4-diphenyl-1,3-butadiene (**1**, 103 mg, 0.500 mmol) in 2.0 mL of EtOAc was added Pd/C (10 wt%, 5 mg, 0.005 mmol). The reaction vessel was purged three times with hydrogen, charged to 50 psi, and then closed off to the source of hydrogen. The reaction was heated under microwave irradiation to 80 °C with 100 W of power and held for 5 min. Upon cooling to ambient temperature, the reaction mixture was filtered through Celite® and condensed to give 105 mg (>99%) of 1,4-diphenylbutane. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.23–7.27$ (m, 4 H), 7.14–7.17 (m, 6 H), 2.62 (t, $J = 6.6$ Hz, 4 H), 1.65 (dt, $J = 7.2, 3.8$ Hz, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 142.66, 128.53, 128.38, 125.77, 35.93, 31.20$. Characterization data is consistent with that of commercially available material.

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