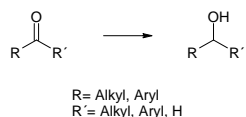


# Reduction of Aldehydes and Ketones Using Solid Supported Borohydride and Microwave Heating

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## Introduction

One very common transformation in organic synthesis is the reduction of aldehydes or ketones to the corresponding primary or secondary alcohols (Scheme 1) using sodium borohydride as hydride donor. This reaction generally generates the product in very high yield. Among the draw-backs are long reaction times, that a large excess of reagent is needed and that the reaction mixture must be extracted in order to separate the inorganic salts from the product.

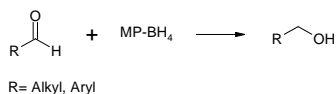


Scheme 1.

We decided to investigate the use of solid supported macroporous borohydride (MP-BH<sub>4</sub>)<sup>1</sup> where the sodium cation is replaced by tetraalkyl ammonium cation which is covalently bonded to cross-linked polystyrene. The inorganic salts are linked to a solid support, and thus the extraction step can be omitted. Further, we wanted to use controlled microwave heating in order to decrease the reaction times generally from hours to minutes.

## Results and discussion

### Reduction of aldehydes



As a reference reaction, we used the reduction of p-Tolualdehyde with 0.5 equiv. MP-BH<sub>4</sub> and methanol as solvent at room temperature.<sup>2</sup> The conversion was 87 % after 3 h, 92 % after 4.5 h and 100 % over night. The product was isolated by filtration, washing of the solids with dichloromethane, concentration and drying. The isolated yield and purity was 95 % and >99 % (by HPLC-MS and <sup>1</sup>H-NMR) respectively. Initial optimisation experiments using microwave heating for 10 minutes on Initiator™ Sixty, revealed that the reaction gives better conversion in methanol or ethanol compared to dichloromethane at 100 °C using 0.50 equiv. MP-BH<sub>4</sub>. Increasing the temperature to 140 °C a lower conversion was obtained and a residual pressure in the reaction vial, probably due to the reagent reacting with the solvent. Further optimisation revealed that if 0.75 equiv. MP-BH<sub>4</sub> was used with a reaction time of 7 minutes in ethanol at 130 °C, complete conversion was obtained. Ethanol was chosen as solvent since it gives lower pressure at elevated temperatures than methanol.

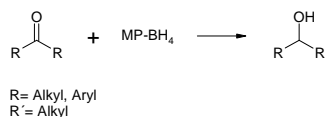
Using these generic conditions a small library was produced (Table 1) using aryl-, alkyl- and α,β-unsaturated aldehydes.

Entry	Aldehyde	Time (min)	HPLC-purity (%)	Yield (%)
1	4-Tolualdehyde	7	100	94
2	4-Methoxybenzaldehyde	10 <sup>a</sup>	97	96
3	4-Chlorobenzaldehyde	7	100	94
4	4-Cyanobenzaldehyde	7	99	94
5	3-Pyridine carboxaldehyde	7	100	99
6	3-Phenoxybenzaldehyde	7	98	94
7	2-Tolualdehyde	7	99	98
8	2-Chlorobenzaldehyde	7	98	96
9	4-Dimethylaminobenzaldehyde	15 <sup>a</sup>	90	99
10	4-(Imidazol-1-yl)benzaldehyde	10 <sup>a</sup>	99	98
11	Cyclohexyl carboxaldehyde	7	97*	98
12	2-Phenylpropionaldehyde	7	100*	91
13	trans-3-(2-Furyl)acrolein	7	87*	85
14	4-Dimethylaminocinnamaldehyde	7	57*	93

Table 1. Reduction of aldehydes.  
a= 1.00 equiv. MP-BH<sub>4</sub> was used. \*Purity by <sup>1</sup>H-NMR.

If benzaldehydes are substituted with strongly electron-donating substituents (entries 2 and 9), prolonged reaction times and 1.00 equiv. MP-BH<sub>4</sub> were needed in order to obtain a good conversion. The material isolated contained mostly product. Where the purity was less than 100 %, for entries 1-12, only starting material was observed in the isolated material. Reduction of α,β-unsaturated aldehydes gave a high extent of saturated alcohol. For entry 13, 12 % of the isolated material was found to be the saturated alcohol. For entry 14, 17 % of saturated alcohol along with 26 % starting material was observed.

### Reduction of ketones



As a reference reaction, we used the reduction of acetophenone with 0.78 equiv. MP-BH<sub>4</sub> and methanol as solvent at room temperature. This reaction is reported to give only 6 % product after 16 h.<sup>2</sup> We started the optimisation with the conditions used for the reduction of aldehydes. Since we could not increase the temperature further, 1.00 equiv. MP-BH<sub>4</sub> was used with a prolonged reaction time of 30 minutes. Complete conversion was then obtained.

Using these generic conditions a small library was produced (Table 2) using aryl-, alkyl- and α,β-unsaturated ketones.

Entry	Ketone	Time (min)	HPLC-purity (%)	Yield (%)
1	Acetophenone	30	99	95
2	4-Bromacetophenone	30	100	95
3	2-Bromacetophenone	30	100	94
4	5-Brom-1-indanone	30	88 <sup>a</sup>	74
5	3,4-Dichloropropiophenone	30	98 <sup>a</sup>	97
6	2-Methoxyacetophenone	30	89	90
7	4-Cyanoacetophenone	30	93 <sup>a</sup>	92
8	5-Methoxytetralone	30	91	99
9	Tetralone	30	89	97
10	1,4-Cyclohexadione mono-ethyleneketal	30	100*	100
11	N-Benzyl-4-piperidone	30	100*	98
12	4-Phenylcyclohexanone	30	100*	97
13	Phenyl-2-butanone	30	82 <sup>b</sup>	91
14	Benzylacetone	30	89	97
15	Ethyl 2-benzylacetoacetate	30	88*	80
16	trans-4-Phenyl-3-buten-2-one	30	52*	86
17	4-[4-(Dimethylamino)phenyl]-but-3-en-2-one	30	54*	95

Table 2. Reduction of ketones.  
a= traces of eliminated byproduct. b= cis/trans-mixture. c= diastereomeric mixture. \*Purity by <sup>1</sup>H-NMR.

Reduction of α,β-unsaturated ketones gave a high extent of saturated alcohol. For entry 16, 42 % of the corresponding saturated alcohol was obtained. For entry 17, 24 % of saturated alcohol along with 22 % starting material was observed.

### General experimental procedure

**Reduction of aldehydes.** To a 2-5 mL microwave reaction vial with 256 mg MP-BH<sub>4</sub> (2.93 mmol/g, 0.75 mmol) was added 3.0 mL ethanol and 1.00 mmol aldehyde. The vial was capped and heated to 130 °C using Initiator for the time stated in Table 1. After cooling, the vial was decapped and the mixture was filtered. The solid material was washed with 10 mL dichloromethane and the solution was concentrated and dried under vacuum. All products were analysed by HPLC-MS and <sup>1</sup>H-NMR.

**Reduction of ketones.** To a 2-5 mL microwave reaction vial with 341 mg MP-BH<sub>4</sub> (2.93 mmol/g, 1.00 mmol) was added 3.0 mL ethanol and 1.00 mmol ketone. The vial was capped and heated to 130 °C for 30 minutes using Initiator. After cooling, the vial was decapped and the mixture was filtered. The solid material was washed with 10 mL dichloromethane and the solution was concentrated and dried under vacuum. All products were analysed by HPLC-MS and <sup>1</sup>H-NMR.

### Conclusion

Reduction of aldehydes and ketones with MP-Borohydride in combination with microwave heating works well. The extractive work-up can be omitted. In most cases no byproducts are formed.

### References:

- Argonaut MP-Borohydride
- Argonaut Technical Notes for MP-Borohydride

<http://www.biotage.com>