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Communication

Microwave-Assisted Solid Reaction: Reduction of Ketones Using Sodium Borohydride

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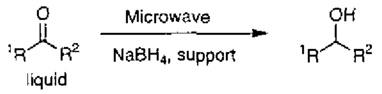
A general and efficient procedure for microwave-assisted reduction of liquid and solid ketones using sodium borohydride without solvents is described. The added support can enhance both the efficiency and chemoselectivity of reduction.

Current environmental and economic demands have generated the need for a paradigm shift in the chemical industry in regard to chemical synthesis. Organic reactions carried out in dry media[1] have recently received attention and have many advantages over solution reactions. Sodium borohydride is widely used as a reducing agent for reduction of aldehydes and ketones in protic[2] or aprotic solvents with Lewis acids or acid resins.[3] NaBH$_4$ reduction of ketones to alcohols in the solid state has also been reported.[4] However, the drawback of this solid state reaction is that it must be kept in a dry box at room temperature for five days, and needs to be stirred once a day.[4] Recently, reduction of aldehydes and ketones by NaBH$_4$-alumina under microwave irradiation has been reported, but no reaction takes place in the absence of alumina.[5] We have developed a novel application of microwave technology to the solid phase peptide synthesis and other chemical reactions,[6] in which we found that under microwave irradiation the solid phase resin will not affect the enhanced-rate of peptide bond formation. We report here the necessity of a solid support for effective reduction of aldehydes and ketones, and the development of a general method to carry out the reduction of ketones with various solid supports using a household microwave.

Table 1. Solid State Reduction of Liquid Ketones with NaBH$_4$ under Microwave



entry	R$_1$	R$_2$	support[a]	ketone/ NaBH$_4$ (equiv)	Time	Conv.[b] (%)
1	C$_6$H$_5$	CH$_3$	None	1:10	5 min	81
2	C$_6$H$_5$	CH$_3$	Celite	1:10	5 min	> 98
3	C$_6$H$_5$	CH$_3$	SiO$_2$	1:10	5 min	> 98
4	C$_6$H$_5$	CH$_3$	Celluose	1:10	5 min	> 98
5	C$_6$H$_5$	CH$_3$	MgSO$_4$	1:10	5 min	> 98
6	C$_4$H$_9$	C$_2$H$_5$	SiO$_2$	1:10	5 min	> 98
7	C$_6$H$_5$	CH$_3$	SiO$_2$	1:1	5 min	> 98
8	C$_6$H$_5$	CH$_3$	Celite	1:1	5 min	> 98
9	C$_6$H$_5$	CH$_3$	MgSO$_4$	1:1	5 min	> 98
10	C$_6$H$_5$	CH$_3$	Celluose	1:1	5 min	> 98

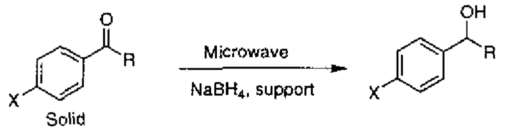
[a] The reactions were carried out with 0.5 mmol of ketones and celite (1.03 g) or SiO$_2$ (1.04 g) or celluose (1.21 g) or MgSO$_4$ (1.37 g).

[b] The conversion based on ketones and their corresponding alcohols was determined with 400 MHz ^{1}H NMR.

In a preliminary test, we used an excess amount of NaBH$_4$ without alumina or any support to reduce acetophenone and found an 81% conversion under microwave irradiation (Table 1, entry 1). We deduced that the powder of excess NaBH$_4$ dispersed the aggregation of ketones and subsequently made a useful contact to provide an efficient reaction. In order to test this hypothesis, we used Celite, SiO$_2$, cellulose, and MgSO$_4$ as a support for the reduction of acetophenone under microwave irradiation and obtained high yields in each reaction (see Table 1, entries 2-6). The alumina is not the only reason to catalyze the reaction, but the dispersion, caused by the solid support, made a useful contact to provide an efficient reaction. Moreover, in the presence of a support the reaction could also proceed very well when using a small excess of NaBH$_4$ (entry 7-10).

For further investigation of the usefulness of the microwave irradiation protocol, various solid ketones were used in the reaction. Results are shown in Table 2. The reduction of solid ketones could also give a good conversion even with no supports (entries 1-3). In the case of benzophenone (Table 2, entry 3), the reduction needed more time and NaBH$_4$[5] to complete the reaction. This lower conversion may be due to a steric effect. It is interesting that when we added cellulose to the solid mixture, this reduction pro-

Table 2. Solid State Reduction of Solid Ketones with $NaBH_4$ under Microwave



entry	R	X	support	ketone/ $NaBH_4$ (equiv)	Time	Conv.[a] (%)
1	C_6H_5	Br	None	1:10	5 min	> 98
2	C_6H_5	OH	None	1:10	5 min	> 98
3	C_6H_5	C_6H_5	None	1:10	5 min	65
4	C_6H_5	C_6H_5	Cellulose[b]	1:10	5 min	> 98
5	C_6H_5	Br	Cellulose[b]	1:1	5 min	> 98
6	C_6H_5	C_6H_5	Cellulose[b]	1:1	5 min	90

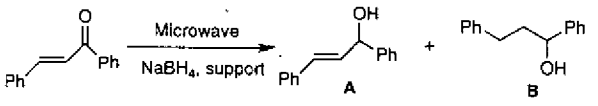
[a] The conversion based on ketones and their corresponding alcohols was determined with 400 MHz ^1H NMR.

[b] The reactions were carried out with 0.5 mmol of ketones and cellulose (1.21 g).

ceeded very well even though using a lower amount of $NaBH_4$ (entries 4-6). Except for easily evaporated or sterically-kindered ketone, according to our experience, there is no big difference between dialiphatic ketone and diaromatic or aromatic aliphatic ketone. In Table 1 and Table 3, we have demonstrated that this reduction of ketone proceeds well no matter what kind of support. Moreover we used an organic support like cellulose to demonstrate the reduction of ketone, not only under inorganic supports but also under organic supports.

We used SiO_2 as a supporting agent to initiate microwave-assisted solid reduction of chalcone, this procedure can improve the chemoselectivity of reduction of chalcone; instead of two products in the ratic of 60:40 of reported procedure.[4]

Table 3. The Chemoselective Reduction of Chalcone Using $NaBH_4$/Support



entry	support[a]	ketone/ $NaBH_4$ (equiv)	Time	A:B[b]
1	None	1:10	5 min	1:1.4
2	Celluose	1:1	5 min	1.4:1[c]
3	SiO_2	1:10	5 min	>98:<2

[a] The amount of support is the same as in Table 1.

[b] The ratio of A and B was determined by NMR.

[c] Crude products included compounds A, B, saturated ketones, and unreacted chalcones.

Microwave heating involves direct absorption of energy by functional groups that bear ionic conductivity or a dipole rotation effect, and this energy is then released to the surrounding solution. This absorption of energy causes the functional groups involved to have higher reactivity with surrounding reactants than when they are simply incubated with the reactants at the same temperature. We suppose those solid supports can be used to disperse the aggregation of ketones and then make the reduction more efficient. The rapid transfer of heat *via* microwave irradiation to shorten the reaction time is more evidence in the case of solid reaction because the heat conducted in solid state is slower than in solution phase.

In conclusion, we have demonstrated that the solid-supported reduction of ketones under microwave irradiation can proceed very well not only with inorganic alumina support but also nonmetal supports. Compared with other solid reduction of ketones, we also developed an efficient alternative for sodium borohydride reduction.

General Procedure for Reduction of Ketones

A mixture of acetophenone (91 mg, 0.5 mmol) or 4'-bromoacetophenone (99 mg, 0.5 mmol), $NaBH_4$ (38 mg, 0.5 mmol), and support (1.4 g) was finely powdered on an agate mortar and pestle. The powder was put into a quartz tube and irradiated with microwave (90% of full power; Tatung microwave oven TMO-110, Tatung Co., Taipei, Taiwan) for 5 min. The product was extracted with ethyl acetate. The organic phase was dried over magnesium sulfate and then concentrated to give pure 1-phenylethanol or 1-(4'-bromophenyl)ethanol.

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Key Words

Microwave-assisted; Ketone; Chemoselectivity.

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7. **1-Phenylethanol** ^{1}H NMR (acetone-d$_6$) δ 1.46 (d, 3H, J = 6.5 Hz), 2.17 (brs, 1H), 4.84 (q, 1H, J = 6.5 Hz), 7.35-7.23 (m, 5H); FAB MS, m/e 122 (M$^+$); **1-(4-Bromophenyl)ethanol** ^{1}H NMR (CDCl$_3$) δ 1.43 (d, 3H, J = 6.6 Hz), 2.03 (brs, 1H, OH), 4.82 (q, 1H, J = 7.3 Hz), 7.21 (d, 2H, J = 8.7 Hz), 7.44 (d, 2H, J = 8.7 Hz); FAB MS, m/e 200 (M$^+$); **1-(4-Hydroxyphenyl)ethanol** ^{1}H NMR (acetone-d$_6$) δ 1.39 (d, 3H, J = 6.4 Hz), 4.13 (d, 1H, J = 3.9 Hz), 4.81-4.75 (m, 1H), 6.80 (d, 2H, J = 8.5 Hz), 7.22 (d, 2H, J = 8.5 Hz); FAB MS, m/e 138 (M$^+$); **Diphenylmethanol** ^{1}H NMR (acetone-d$_6$) δ 4.98 (d, 1H, J = 3.9 Hz), 5.86 (d, 1H, J = 3.9 Hz), 7.27-7.23 (m, 2H), 7.47-*7.44 (m, 4H); FAB MS, m/e 184 (M$^+$);* ***Trans*-1,3-diphenyl-prop-2-en-1-ol** ^{1}H NMR (acetone-d$_6$) δ 4.76 (d, 1H, J = 4.0 Hz), 5.43-5.41 (m, 1H), 6.48 (dd, 1H, J = 6.4, 5.8 Hz), 6.76 (d, 1H, J = 15.8 Hz), 7.58-7.26 (m, 10H); FAB MS, m/e 186 (M$^+$); **1,3-Diphenylprop-1-ol** ^{1}H NMR (acetone-d$_6$) δ 2.20-2.15 (m, 2H), 2.76-2.66 (m, 3H), 4.66 (dd, 1H, J = 5.4, 10.5 Hz), 7.39-7.20 (m, 10H); FAB MS, m/e 188 (M$^+$).