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The Microwave-Assisted Solventless Reduction of Aldehydes and Ketones Using Silica Supported Sodium Borohydride

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Abstract The rapid, solventless reduction of aldehydes and ketones is described. Using sodium borohydride supported in silica gel and microwave irradiation gave the corresponding alcohols in high yields, with reduced reaction time and less waste compared to the conventional reductions. The percent conversion was dependent on the steric hindrance within the carbonyl compound and not directly related to the charge on the carbonyl carbon.

Keywords Solid-State synthesis, Microwave-Assisted, Reductions, Solventless

1. Introduction

We are reporting the microwave-assisted reduction of various carbonyl compounds using solid-state supported sodium borohydride. This reaction method is a possible alternative and complementary to the traditional reduction using metal borohydrides in solution. The reduction of carbonyl groups by sodium borohydride is a common reaction in organic chemistry. [1] Sodium borohydride is a relatively mild reducing agent that allows for selectivity of reduction site and more versatile than other non-borohydride reducing agents with regards to solvents and reactants that can be used. [2, 3] The usefulness of sodium borohydride as a reducing agent is generally limited by the reaction time necessary to complete the reductions. Most sodium borohydride reductions take several hours for completion. [2, 3] It was reported that a solvent-free procedure required more than five days for the reduction of a cyclohexanone derivative in modest (54%) yield. [4]

Microwave-assisted synthesis has been shown to accelerate organic reactions and may be used as an alternative to conventional heating methods. [1-3, 5] Current theory relates the reaction acceleration to the ability of microwaves to more evenly and rapidly heat reactants and reagents at the molecular level. [5, 6] A wide variety of microwave-assisted reactions have been reported, but the overwhelming majority are performed in solution. [5, 6] Solvent-free techniques employ neat reactants and/or reagents that are supported on a solid matrix. Solid-support techniques require the use of less organic solvents and in some cases, allow for recycling of the support material. Microwave-assisted solvent-free reactions have been shown to both decrease reaction times and increase product yields. [3, 5, 7] Solvent-free reactions can also be conducted in open vessels, will produce less pressure, [2] and are more easily scaled-up for production than solvent-based microwave reactions. [8] These methods are known to decrease the environmental impact of the reaction. [2, 8, 9]

There are several examples of the microwave-assisted reduction of ketone and aldehyde compounds by sodium borohydride supported on alumina in the literature. [3, 2, 10, 8, 11] Prior work by our group has previously demonstrated the microwave-assisted reduction of cyclohexanone to cyclohexanol using sodium borohydride supported on a silica matrix. [12] Herein we wish to report the versatility of microwave-assisted solid-supported sodium borohydride reductions for ketone and aldehyde compounds with varying degrees of steric hindrance and a variety of functional groups. (**Figure 1**)

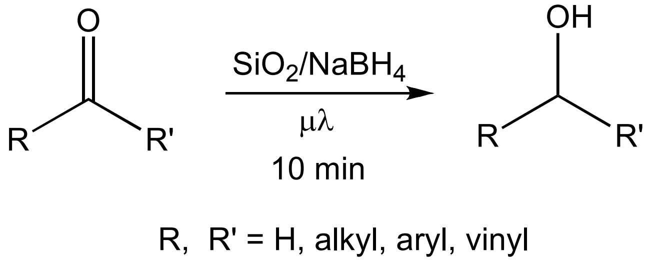

Figure 1. Reaction scheme for the reduction of carbonyl compounds to corresponding alcohols

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2. Experimental

2.1. Materials and Equipment

All reactant ketones and aldehydes, diethyl ether, silica gel, and sodium borohydride were purchased from Aldrich Chemical Company and used as received. The reactions were run in 50 mL PTFE-lined, glass microwave reaction vessels and irradiated with a Milestone START microwave labstation. The products were characterized by ^{1}H NMR spectroscopy and GC-MS and compared to authentic samples. GC-MS analysis was conducted on an Agilent 5977A Extractor XL MSD with a chemical ionization detector. Split injections with a 100:1 split ratio was used. The GC was fitted with an HP-5 (5% phenyl: 95% methyl silicone) column (dimensions: 30 m x 0.32 mm; flow rate: 1.64 mL/min; Injector temperature: 250°C; Oven temperature: 150°C; Detector temperature: 290°C). ^{1}H NMR spectra were recorded on a JEOL 400 MHz spectrometer and spectra were obtained in $CDCl_3$. Carbonyl charges were determined using Spartan Student v. 6.1.4 measuring the energy at the ground state with the B3LYP 6-31G* calculation.

2.2. General Procedure

A mixture of sodium borohydride (200 mg) and silica gel (400 mg) were combined and ground with a mortar and pestle to produce the supported reducing agent. The sodium borohydride/silica mixture was combined with 600 mmol of the aldehyde or ketone in a 50 mL PTFE-lined, glass microwave reaction vessel and mixed thoroughly. The cap was securely fastened, placed in the microwave, and irradiated at 75% power (900 W) for 10 minutes. The alcohol product was extracted from the solid support with 5 mL diethyl ether and gravity filtered through a fritted funnel. The solvent was removed *in vacuo* to give the alcohol product. Percent conversion was determined by GC and product identification confirmed by 1H-NMR by comparison to an authentic sample.

Table 1. Percent conversion for the reduction of aldehydes and ketones by solid-phase supported $NaBH_4$ and calculated charges on the carbonyl carbon

Entry	Aldehyde/Ketone	Alcohol Product	Percent Conversion	Charge On Carbonyl Carbon, e^-
1	propanal	1-propanol	94%	0.471
2	butanal	1-butanol	92%	0.487
3	hexanal	1-hexanol	96%	0.491
4	*trans*-2-hexenaldehyde	*trans*-2-hexen-1-ol	88%	0.579
5	*trans*-cinnamaldehyde	*trans*-2-cinnamyl alcohol	38%	0.520
6	propanone	isopropanol	98%	0.978
7	2-butanone	2-butanol	91%	0.863
8	2-pentanone	2-pentanol	92%	0.906
9	3-pentanone	3-pentanol	92%	0.733
10	4-methyl-2-pentanone	4-methyl-2-pentanol	87%	0.946
11	2-hexanone	2-hexanol	95%	1.018
12	4-heptanone	4-heptanol	94%	0.732
13	2,6-dimethyl-4-heptanone	2,6-dimethyl-4-heptanol	63%	0.877
14	cyclopentanone	cyclopentanol	93%	0.787
15	cyclohexanone	cyclohexanol	96%	0.792
16	2-methylcyclohexanone	2-methylcyclohexanol	82%	0.597
17	3-methylcyclohexanone	3-methylcyclohexanol	90%	0.786
18	2,6-dimethylcyclohexanone	2,6-dimethylcyclohexanol	76%	0.422
19	benzaldehyde	benzyl alcohol	99%	0.386
20	2-methylbenzaldehyde	2-methylbenzyl alcohol	85%	0.453
21	3-methylbenzaldehyde	3-methylbenzyl alcohol	82%	0.445
22	4-methylbenzaldehyde	4-methylbenzyl alcohol	89%	0.445
23	2-methoxybenzaldehyde	2-methoxybenzyl alcohol	88%	0.496
24	3-methoxybenzaldehyde	3-methoxybenzyl alcohol	83%	0.427
25	4-methoxybenzaldehyde	4-methoxybenzyl alcohol	84%	0.476
26	3-chlorobenzaldehyde	3-chlorobenzyl alcohol	75%	0.413
27	acetophenone	methylbenzyl alcohol	98%	0.768
28	4-methoxyacetophenone	4-methoxy-α-methylbenzyl alcohol	91%	0.863
29	benzophenone	benzhydrol	82%	0.433
30	pincacolone	pinacol	84%	0.695

3. Results and Discussion

Reaction Yields Different aldehyde and ketone compounds were reduced by sodium borohydride supported in a silica matrix with the assistance of microwave irradiation in excellent yields (**Table 1**). Percent conversion was greater than 70% for twenty-eight of the thirty ketones and aldehydes studied. The only exceptions were *trans*-cinnamaldehyde where the carbonyl group is highly conjugated and the sterically hindered carbonyl group of 2,6-dimethyl-4-heptanone. All microwave-assisted reductions proceeded to completion within ten minutes. Allowing the reaction to continue for additional time did not result in noticeable increases in yield. The silica may be washed with methanol followed by water and then dried in an oven to be reloaded with sodium borohydride. Recycled silica showed no difference in its ability to support the reducing agent.

Mechanism Sterics and Carbonyl Charges Substitution on the α-carbon near the carbonyl group being reduced increased the steric hindrance and appears to affect the percent conversion for the reduction. For example, the aliphatic acylic 2,6-dimethyl-4-heptanone gave a lower percent conversion (63%) than the less sterically hindered 4-heptanone (94%). The cyclic ketones 2,6-dimethylcyclohexanone (76%) 2-methylcyclohexanone (82%), 3-methylcyclohexanone (90%), and cyclohexanone (96%) all followed the same trend. This trend was also observed for the aromatic substituted ketones, comparing benzophenone (82%) and acetophenone (98%) showed that less steric hindrance resulted in greater conversion to the alcohol. The calculated charge on the carbonyl carbon showed no correlation with the percent conversion. For instance, even though there is a significant calculated charge difference between the carbonyl carbons of 2-hexanone and 4-heptanone the percent conversions for both are essentially identical. If the percent conversion was dependent on charge, with all other considerations being equal, the more positively charged carbonyl carbon should, in theory, give the highest percent conversion. The is also seen for the aromatic aldehydes and ketones. Both benzophenone and pinacalone have the same percent conversion even though there is a large charge difference on the carbonyl carbons. It appears that sterics is the most significant factor that influences percent conversion with little or no contribution from the electrostatic interactions between the positively charged carbonyl carbon and hydride ion. This is consistent with what has been reported by others and indicates the same mechanism for reduction occurs in both solution and under solventless conditions. [13-17]

4. Conclusions

We have developed a versatile method for the microwave-assisted reduction of aldehydes and ketones using sodium borohydride. Reactions are completed within ten minutes and typically result in a high percent conversion. The resulting alcohols are easily isolated and the silica support can be refreshed and reused for subsequent reductions.

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