



## TiO<sub>2</sub> as an Efficient Catalytic Surface for Reduction of Carbonyl Compounds with NaBH<sub>4</sub> under Solvent-free, Solid-gel and Microwave Irradiation

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### ABSTRACT

Structurally different carbonyl compounds such as aldehydes, ketones,  $\alpha,\beta$ -unsaturated enals and enones,  $\alpha$ -diketones and acyloins were reduced efficiently by NaBH<sub>4</sub>/TiO<sub>2</sub> system under solvent-free, solid-gel and microwave irradiation. The chemoselective reduction of aldehydes over ketones was achieved successfully by NaBH<sub>4</sub>/TiO<sub>2</sub> system at solvent-free condition. In addition, regioselectivity and exclusive 1,2-reduction of conjugated carbonyl compounds to their corresponding allylic alcohols in high to excellent yields was accomplished successfully with this reducing system.

**Key words:** NaBH<sub>4</sub>, TiO<sub>2</sub>, Solvent-free, Solid-gel, Microwave.

### INTRODUCTION

It is over fifty years that NaBH<sub>4</sub> has been widely recognized as the reagent of choice for the reduction of carbonyl compounds in protic solvents<sup>1</sup>. Over the past two decades, the utility of sodium borohydride has been greatly expanded and different techniques and modifications have been reported for this reagent to reduce organofunctional groups in various solvents. These modifications may involve replacement of one or more hydrides with other substituents<sup>2</sup>, change of the sodium cation to other metal<sup>3</sup>, quaternary ammonium and phosphonium cations<sup>4</sup>, a concurrent cation and

hydride exchange<sup>5</sup>, ligand-metal borohydrides<sup>6,7</sup>, combination of borohydrides with Lewis acids, additives and mixed-solvents systems<sup>8,9</sup>, and finally use of polymers or solid beds for supporting the borohydride species<sup>10</sup>. In this context, the applications of modified borohydride agents in organic synthesis have been reviewed extensively<sup>6,11</sup>.

Nowadays, the simplification of reaction protocols and minimizing the use of auxiliaries is an important paradigm in green chemistry. Working without solvents gives the potential for a simpler process, smaller plants, and eliminates the energy

costs of removal, recycling and eventual disposal of waste solvents. So, several techniques and protocols for the efficient use of solvent-free reactions have been reported in organic synthesis<sup>12</sup>. Literature review shows that the reduction of carbonyl compounds with NaBH<sub>4</sub> at solvent-free condition in the presence or absence of mineral solid supports has been rarely investigated: e.g., the solid state reduction of ketones was achieved by mixing the carbonyl compounds with sodium borohydride and storing the mixture in a dry box for five days<sup>13</sup>. The major shortcoming of this method is that it takes a long time for any practical application. In addition, the need for large amounts of NaBH<sub>4</sub> (tenfold) is a serious limitation in this method. Varma reported that reduction of carbonyl compounds was accomplished in solid state with NaBH<sub>4</sub> supported on dry Al<sub>2</sub>O<sub>3</sub> under microwave irradiation<sup>14</sup>. Though the method is fast in the reduction of aldehydes, however, in the case of ketones the need for large amounts of NaBH<sub>4</sub> (eightfold), moderate yields of products, the slow rate of reductions and low regioselectivity in the reduction of conjugated carbonyl compounds are the major limitations of this protocol. Microwave-assisted reduction of two liquid ketones (acetophenone and ethylphenyl ketone) with NaBH<sub>4</sub>/dry SiO<sub>2</sub> system was also reported in solid state, however, the behavior of other carbonyl compounds was not further documented<sup>15</sup>. This combination system suffers from the acidic surface of silica gel and this condition decomposes NaBH<sub>4</sub> vigorously with the evolution of hydrogen gas. In order to overcome the above mentioned limitations specially at NaBH<sub>4</sub>/dry SiO<sub>2</sub> and NaBH<sub>4</sub>/dry Al<sub>2</sub>O<sub>3</sub>/microwave systems and introduce an effective and practical synthetic protocol for the reduction of carbonyl compounds with NaBH<sub>4</sub> through minimizing or avoiding of solvents, in this paper we wish to report wet TiO<sub>2</sub> as a perfect media to perform the mild, selective and efficient reduction of carbonyl compounds with NaBH<sub>4</sub> under solvent-free, solid-gel and microwave irradiation.

## EXPERIMENTAL

All substrates and reagents were purchased from commercially sources with the best quality and used without further purification. TiO<sub>2</sub> was purchased from Merck company. IR and <sup>1</sup>H NMR spectra were recorded on PerkinElmer FT-IR RXI and

300 MHz Bruker spectrometers, respectively. Agilent gas chromatograph equipped with a FID detector was used for this study. The products were characterized by their <sup>1</sup>H NMR or IR spectra and comparison with authentic samples (melting or boiling points). Organic layers were dried over anhydrous sodium sulfate. All yields referred to isolated pure products. TLC was applied for the purity determination of substrates, products and reaction monitoring over silica gel 60 F<sub>254</sub> aluminum sheet.

### A Typical Procedure for Reduction of Carbonyl Compounds with NaBH<sub>4</sub>/Wet TiO<sub>2</sub> System at Solvent-Free Condition

In a round-bottomed flask (5 mL) charged with TiO<sub>2</sub> (0.5 g), H<sub>2</sub>O (0.1 g) was added and the mixture was stirred with a magnetic stirrer to produce wet TiO<sub>2</sub> (0.5 g, 20% m/m). To the prepared wet TiO<sub>2</sub>, benzaldehyde (0.106 g, 1 mmol) was added and the resulting mixture was then stirred for 5 min. Afterward, NaBH<sub>4</sub> (0.039 g, 1 mmol) as a fine powder was added to the reaction mixture and the mixture was stirred for 15 min at room temperature. The progress of the reaction was monitored by TLC (eluent; CCl<sub>4</sub>/Et<sub>2</sub>O: 5/2). At the end of reaction, the mixture was washed three times with CH<sub>2</sub>Cl<sub>2</sub> (3 × 8 mL) and the combined washing solvents were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Evaporation of the solvent and a short column chromatography of the resulting crude material over silica gel (eluent; CCl<sub>4</sub>/Et<sub>2</sub>O: 5/2) afford the pure colorless liquid benzyl alcohol (0.104 g, 96%, Table 1, method A).

### A Typical Procedure for Competitive Reduction of Aldehydes over Ketones with NaBH<sub>4</sub>/wet TiO<sub>2</sub> System at Solvent-Free Condition

To a round-bottomed flask (5 mL) charged with wet TiO<sub>2</sub> (0.5 g, 20% m/m), benzaldehyde (0.106 g, 1 mmol) and acetophenone (0.12 g, 1 mmol) was added and the mixture was stirred with a magnetic stirrer for 5 min. NaBH<sub>4</sub> (0.039 g, 1 mmol) as a fine powder was added to the reaction mixture and it was stirred at room temperature. After 15 min, the mixture was washed three times with CH<sub>2</sub>Cl<sub>2</sub> (3 × 8 mL) and the combined washing solvents were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Evaporation of the solvent and a short column chromatography of the resulting crude material over silica gel (eluent; CCl<sub>4</sub>/Et<sub>2</sub>O: 5/2) give the pure liquid benzyl alcohol as a sole product and acetophenone as an intact material (Table 4, entry 1).

### A Typical Procedure for Reduction of Carbonyl Compounds with NaBH<sub>4</sub>/Wet TiO<sub>2</sub> System in a Solid-Gel Media

In a round-bottomed flask (5 mL) charged with wet TiO<sub>2</sub> (0.5 g, 20% m/m), CH<sub>3</sub>CN (0.5 mL) was added and the mixture was stirred with a magnetic stirrer to produce a solid-gel media. To the resulting mixture, benzophenone (0.182 g, 1 mmol) was added and the mixture was continued to stirring for 5 min. NaBH<sub>4</sub> (0.076 g, 2 mmol) as a fine powder was added to the reaction mixture and the mixture was stirred at room temperature for 60 min. TLC was monitored the progress of the reaction (eluent; CCl<sub>4</sub>/Et<sub>2</sub>O: 5/2). At the end of reaction, the mixture was washed three times with CH<sub>2</sub>Cl<sub>2</sub> (3 × 8 mL) and the combined washing solvents were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Evaporation of the solvent and a short column chromatography of the resulting crude material over silica gel (eluent; CCl<sub>4</sub>/Et<sub>2</sub>O: 5/2) give the pure white crystalline benzhydrol (0.171 g, 96%, Table 2, method B).

### A Typical Procedure for Microwave-Assisted Reduction of Carbonyl Compounds with NaBH<sub>4</sub>/Wet TiO<sub>2</sub> System

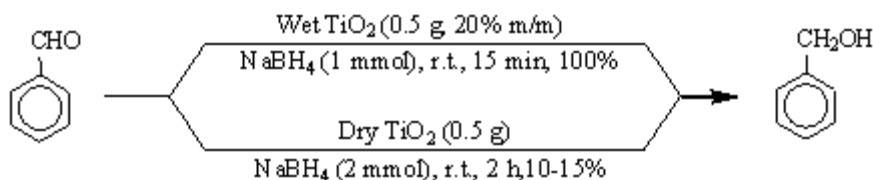
In a round-bottomed flask (5 mL), a mixture of wet TiO<sub>2</sub> (1 g, 100% m/m), acetophenone (0.12 g, 1 mmol) and NaBH<sub>4</sub> (0.078 g, 2 mmol) was prepared. The reaction flask was irradiated with microwaves (300 W) for 2 min. The progress of the reaction was monitored by TLC (eluent; CCl<sub>4</sub>/Et<sub>2</sub>O: 5/2). At the end of reaction, the mixture was washed three times with CH<sub>2</sub>Cl<sub>2</sub> (3 × 8 mL) and the

combined washing solvents were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Evaporation of the solvent and a short column chromatography of the resulting crude material over silica gel (eluent; CCl<sub>4</sub>/Et<sub>2</sub>O: 5/2) afford the pure colorless liquid 1-phenylethanol (0.119 g, 97%, Table 2).

## RESULTS AND DISCUSSION

### Reduction at Solvent-Free and Solid-Gel Conditions

Solvent-free reactions promise to be an essential facet of green chemistry. This type of organic reactions possesses some advantages over traditional reactions in organic solvents<sup>12</sup>. Continuation of our research program directed to the application of modified borohydride agents in organic synthesis<sup>6-8</sup> and the lack of information for the use of NaBH<sub>4</sub>/wet TiO<sub>2</sub> system in organic synthesis encouraged us to study the influence of adsorbed water on the surface of TiO<sub>2</sub> on the rate of reduction of carbonyl compound with NaBH<sub>4</sub> under solvent-free and solid-gel conditions. We first examined the solvent-free protocol. The room temperature reduction of benzaldehyde with two molar equivalents of NaBH<sub>4</sub> and 0.5 g of dry TiO<sub>2</sub> was carried out with 10-15% conversion within 2 h. This reaction in the presence of wet TiO<sub>2</sub> (prepared by simply mixing a small amount of water with TiO<sub>2</sub>) was dramatically accelerated and completed with one molar equivalent of NaBH<sub>4</sub> within 15 min (Scheme 1).



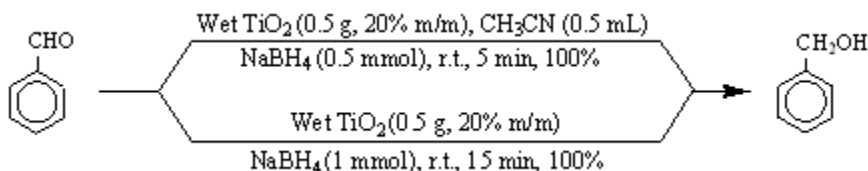
Scheme 1:

The optimization experiments showed that using one molar equivalent of NaBH<sub>4</sub> in the presence of wet TiO<sub>2</sub> (20% m/m, mass ratio) was the optimal for complete reduction of PhCHO at room temperature. This optimal condition was

applied for the reduction of structurally different aliphatic and aromatic aldehydes (method A). The efficiency of reductions was excellent and the corresponding primary alcohols were obtained in 88-98% yields within 5-35 min (Table 1). The

procedure of reduction was easy: a simply mixing and stirring the reaction components (aldehyde,  $\text{NaBH}_4$  and wet  $\text{TiO}_2$ ) at room temperature was produced the product alcohol in the appropriate time.

We also found that by adding a small amount of  $\text{CH}_3\text{CN}$  (0.5 mL) into wet  $\text{TiO}_2$  (20% m/m) and performing the reduction of benzaldehyde with 0.5 molar equivalent of  $\text{NaBH}_4$  in a solid-gel media (method B), the rate of reduction was extremely



**Scheme 2:**

increased and the reaction was completed in 5 minute. (Scheme 2) (Table 1).

The efficiency of solid-gel protocol was further examined by the reduction of structurally different aliphatic and aromatic aldehydes with  $\text{NaBH}_4$ / wet  $\text{TiO}_2$  (20% m/m) system in 0.5 mL of  $\text{CH}_3\text{CN}$ . All reductions were completed within 3-10 min (Table 1, method B). Comparison of the results shows that reductions in method B is faster than those in method A, however, the efficiency of both systems is nearly the same.

At the next attempt, we turned our attention into solvent-less reduction of ketones, acyloins and  $\alpha$ -diketones with sodium borohydride. Less reactivity of ketones relative to aldehydes, led us to perform reductions with two molar equivalents of  $\text{NaBH}_4$  at room temperature or in an oil bath at 70-75°C (method A). Table 2 shows that aromatic or more hindered ketones (entries 1-4), acyloins and  $\alpha$ -diketones (entries 15-17) exhibited low reactivity towards the protocol even in higher temperature, however, 3-acetylpyridine (entry 5) as the same of aliphatic ketones (entries 10-14) showed a higher reactivity at room temperature. We thought that less reactivity of ketones and their low interactions with the reducing agent in solid state created the low-moderate efficiency in method A. We enhanced the efficiency of reductions using the solid-gel protocol by adding 0.5 mL of  $\text{CH}_3\text{CN}$  into wet  $\text{TiO}_2$  (20% m/m) and performed the reductions with 1-2 molar equivalents of  $\text{NaBH}_4$  at room temperature (method

B). The reactions were completed within 20-60 min in high to excellent yields of products (91-98%) (Table 2). Method B again showed a faster reduction rates than method A.

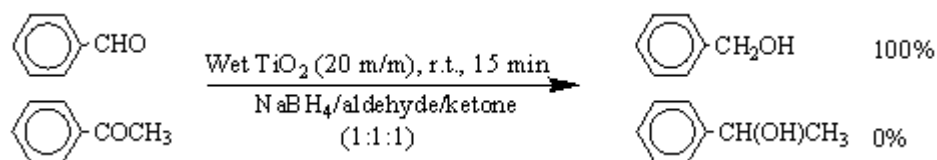
The further utility of  $\text{NaBH}_4$ / wet  $\text{TiO}_2$  system was investigated with regioselective 1,2-reduction of  $\alpha,\beta$ -unsaturated enals and enones. The selectivity was examined with the reduction of cinnamaldehyde by  $\text{NaBH}_4$ /wet  $\text{TiO}_2$  (20% m/m) system. The reduction was carried out with 1 molar equivalents of  $\text{NaBH}_4$  at room temperature under solvent-free condition (method A). The reaction was completed in 15 min and cinnamyl alcohol was obtained with a perfect regioselectivity in 95% yield (Table 3). This procedure was also applied for the reduction of citral in 15 min and geraniol was obtained in 94% yield (Table 2, entry 4).

The solvent-free reduction of conjugated enones was also examined by  $\text{NaBH}_4$ / wet  $\text{TiO}_2$  (20% m/m) system (method A). The reductions were carried out with 2 molar equivalents of  $\text{NaBH}_4$  in an oil bath at 70-75 °C. Table 3 shows that though the yields of products in method A were low to moderate, however, only 1,2-reduction manner was observed in the reactions. This situation motivated us to perform the reductions in a solid-gel media (method B). Reduction of conjugated aldehydes and ketones were carried out by  $\text{NaBH}_4$ / wet  $\text{TiO}_2$  (20% m/m) system in 0.5 mL of  $\text{CH}_3\text{CN}$  at room temperature. The reactions were completed with 0.5-2.0 molar equivalents of  $\text{NaBH}_4$  and the corresponding allylic

alcohols were obtained within 5-60 min in excellent yields and regio-selectivity (Table 3).

The chemoselective reduction of one functional group without affecting the other one is a well-known strategy for preparing of the molecules with ever-increasing complexity in organic synthesis. This subject is of great interest<sup>16</sup> and

numerous modified borohydride agents have been reported for this achievement<sup>6-8,17</sup>. Since under the defined conditions, reduction of aldehydes and ketones by NaBH<sub>4</sub>/wet TiO<sub>2</sub> (20% m/m) system at solvent-free condition was temperature-dependent, we thought that this system can have a chemoselectivity towards reduction of aldehydes over ketones. This fact was demonstrated with the



**Scheme 3:**

selective reduction of benzaldehyde in the presence of aceto-phenone using one molar equivalent of NaBH<sub>4</sub> at room temperature (Scheme 3).

Chemoselectivity of the reduction was excellent and benzyl alcohol was obtained as a sole product besides acetophenone as an intact material (Table 4, entry 1). The usefulness of this protocol was further examined with the reduction of benzaldehyde over benzophenone and heptanal versus cyclohexanone (Table 4, entries 2,3). We again observed that the chemoselectivity was perfect or nearly the so. The chemoselective reduction of  $\alpha,\beta$ -unsaturated enals and enones was investigated successfully with the selective reduction of cinnamaldehyde versus benzalacetone or  $\alpha$ -ionone, and citral over  $\beta$ -ionone (Table 4, entries 3-5). Investigation of the results exhibited an excellent chemoselectivity for NaBH<sub>4</sub>/wet TiO<sub>2</sub> (20% m/m) system under solvent-free condition.

#### Reduction under Microwave Irradiation

Nowadays, microwave irradiation as an unconventional energy source has been widely used to accomplish many kinds of chemical reactions and numerous reviews and papers demonstrated its importance<sup>18</sup>. In this context and to explore the synthetic utility of NaBH<sub>4</sub>/wet TiO<sub>2</sub> system in the reduction of carbonyl compounds,

we decided to couple the solvent-free protocol with microwave irradiation in order to study the influence of adsorbed water on the surface of TiO<sub>2</sub> for transferring the electromagnetic energy to perform reduction reactions.

In this investigation, we used a household domestic microwave oven to perform reduction of benzaldehyde with 0.5 molar equivalent of NaBH<sub>4</sub> in the presence of wet TiO<sub>2</sub> (40% m/m). The reduction was taken place effectively in 20 sec under microwave irradiation (300 W). This observation led us to investigate the reducibility of aliphatic and aromatic aldehydes NaBH<sub>4</sub>/wet TiO<sub>2</sub> system under microwave irradiation. The reactions were carried out with 0.5-1 molar equivalents of NaBH<sub>4</sub> in the presence of NaBH<sub>4</sub>/wet TiO<sub>2</sub> (40-80% m/m) under microwave irradiation (300 W). Completion of the reactions was taken place within 20-40 sec and the corresponding primary alcohols were obtained in 86-98% yields (Table 1).

The reducibility of ketones including acylolins and  $\alpha$ -diketones with NaBH<sub>4</sub>/wet TiO<sub>2</sub> system was also examined under microwave irradiation. The reduction of acetophenone was taken place with one molar equivalent of NaBH<sub>4</sub> in the presence of wet TiO<sub>2</sub> (100% m/m) under microwave irradiation (300 W). The reaction was completed in two min and 1-phenylethanol was obtained in 97% yield. The reduction of structurally

Table 1. Reduction of Aldehydes with NaBH<sub>4</sub>/Wet TiO<sub>2</sub> System under Solvent-Free, Solid-Gel and Microwave Irradiation

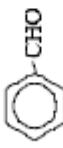
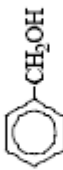
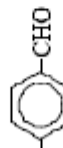
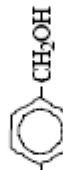
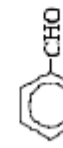

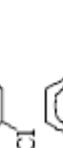

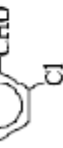

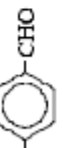
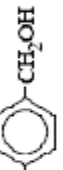
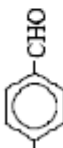


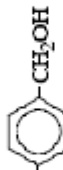
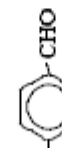
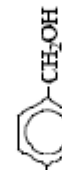
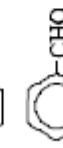
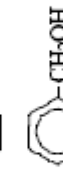

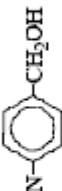

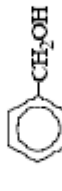
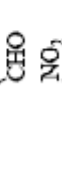
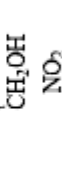

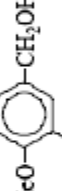


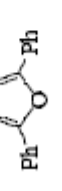
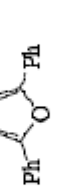
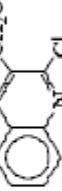
Entry	Substrate	Product	Solvent-free and solid-gel			Microwave irradiation <sup>c</sup>				
			Method <sup>a</sup>	Molar ratio NaBH <sub>4</sub> /Subs.	Time/min	Yield/% <sup>b</sup>	Molar ratio NaBH <sub>4</sub> /Subs.	Wet %	Time/sec	Yield/% <sup>b</sup>
1			(A)	1:1	15	96	0.5:1	40	20	95
			(B)	0.5:1	5	95				
2			(A)	1:1	5	98	0.5:1	80	40	98
			(B)	0.5:1	5	96				
3			(A)	1:1	5	95	0.5:1	80	40	93
			(B)	0.5:1	5	97				
4			(A)	1:1	10	94	0.5:1	80	40	93
			(B)	0.5:1	5	97				
5			(A)	1:1	25	98	0.75:1	80	40	97
			(B)	0.75:1	10	98				
6			(A)	1:1	30	98	0.75:1	80	40	96
			(B)	0.75:1	10	98				
7			(A)	1:1	10	95	0.5:1	40	30	93
			(B)	0.5:1	10	95				
8			(A)	1:1	25	90	0.75:1	40	60	90
			(B)	0.75:1	8	94				
9			(A)	1:1	5	94	0.5:1	40	20	97
			(B)	0.5:1	3	97				
10			(A)	1:1	5	95	0.5:1	80	40	95
			(B)	0.5:1	3	97				

Table 1. (Continued)

11			(A) (B)	1:1 0.5:1	5 3	94 97	0.5:1	40	30	98
12			(A) (B)	1.5:1 1:1	35 5	96 97	1:1	40	30	93
13			(A) (B)	1:1 0.75:1	10 5	95 95	0.75:1	40	30	95
14			(A) (B)	1.5:1 1:1	15 5	95 98	1.5:1	80	40	90
15			(A) (B)	1:1 0.5:1	5 5	97 97	0.5:1	40	30	94
16			(A) (B)	1:1 0.5:1	5 3	89 91	0.5:1	40	30	89
17		(A) (B)	1:1 0.5:1	5 3	88 93	0.5:1	40	30	86	

<sup>a</sup> Method A: the reactions were carried out in the presence of wet TiO<sub>2</sub> (0.5 g, 20% m/m) at room temperature under solvent-free condition; Method B: the reactions were carried out in the presence of wet TiO<sub>2</sub> (0.5 g, 20% m/m) and 0.5 ml of CH<sub>3</sub>CN at room temperature in a solid-gel media; <sup>b</sup> Yields refer to isolated pure products; <sup>c</sup> The reactions were irradiated with microwaves (300 W) in the presence of TiO<sub>2</sub> (0.5 g) at the defined wet %.

Table 2. Reduction of Ketones with NaBH<sub>4</sub>/Wet TiO<sub>2</sub> System under Solvent-Free, Solid-Gel and Microwave Irradiation

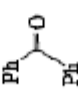
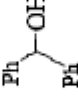
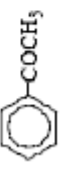

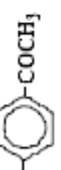

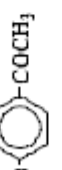

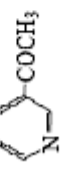

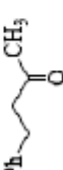

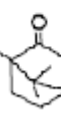

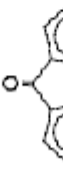



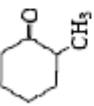
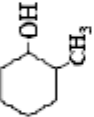
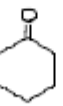
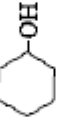


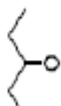
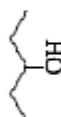


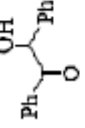
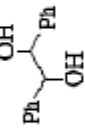
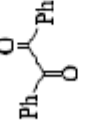
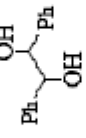
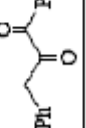
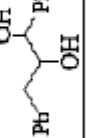
Entry	Substrate	Product	Solvent-free and solid-gel			Microwave irradiation <sup>d</sup>					
			Method <sup>a</sup>	Molar ratio NaBH <sub>4</sub> /Subs.	Condition <sup>b</sup>	Time/min	Yield/% <sup>c</sup>	Molar ratio NaBH <sub>4</sub> /Subs.	Wet %	Time/sec	Yield/% <sup>c</sup>
1			(A)	2:1	Oil bath	60	30	2:1	100	120	95
			(B)	2:1	RT	60	96				
2			(A)	2:1	Oil bath	60	40	2:1	100	120	97
			(B)	2:1	RT	50	95				
3			(A)	2:1	Oil bath	60	50	2:1	100	120	97
			(B)	2:1	RT	50	94				
4			(A)	2:1	Oil bath	60	25	2:1	100	120	96
			(B)	2:1	RT	60	93				
5			(A)	2:1	RT	60	97	1:1	40	20	92
			(B)	1.5:1	RT	30	96				
6			(A)	2:1	RT	60	96	1:1	100	120	94
			(B)	2:1	RT	45	96				
7			(A)	2:1	RT	60	98	2:1	100	60	92
			(B)	2:1	RT	40	92				
8			(A)	2:1	Oil bath	60	60	2:1	100	120	95
			(B)	2:1	RT	60	93				
9			(A)	2:1	Oil bath	60	50	2:1	100	60	96
			(B)	2:1	RT	50	91				

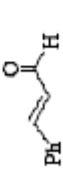

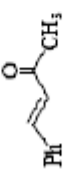

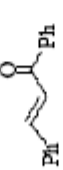
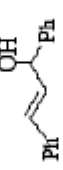
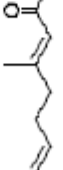
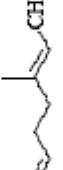
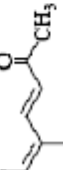



Table 2. (Continued)

10			(A) (B)	2:1 1:1	RT RT	50 30	97 92	1:1	40	40	90
11			(A) (B)	2:1 1:1	RT RT	50 20	91 90	1:1	40	40	92
12			(A) (B)	2:1 1:1	RT RT	50 20	96 97	1:1	100	60	94
13			(A) (B)	2:1 1:1	RT RT	50 20	83 91	1:1	40	40	85
14			(A) (B)	2:1 1:1	RT RT	50 20	93 98	1:1	40	40	85
15			(A) (B)	2:1 1:1	Oil bath RT	60 45	70 98	2:1	100	120	96
16			(A) (B)	2:1 2:1	Oil bath RT	60 60	55 97	2:1	100	120	94
17			(A) (B)	2:1 2:1	Oil bath RT	60 60	45 96	2:1	100	120	90

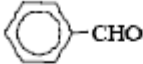
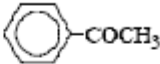
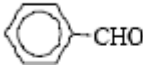


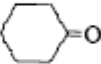
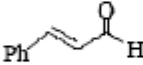
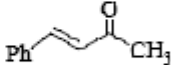
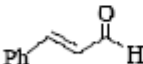
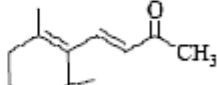
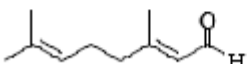
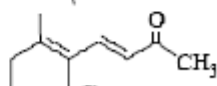
<sup>a</sup> Method A: the reactions were carried out in the presence of wet TiO<sub>2</sub> (0.5 g, 20% m/m) under solvent-free condition; Method B: the reactions were carried out in the presence of wet TiO<sub>2</sub> (0.5 g, 20% m/m) and 0.5 ml of CH<sub>3</sub>CN in a solid-gel media; <sup>b</sup> the temperature of oil bath was 70-75 °C; <sup>c</sup> Yields refer to isolated pure products; <sup>d</sup> The reactions were irradiated with microwaves (300 W) in the presence of TiO<sub>2</sub> (0.5 g) at the defined wet %.

Table 3. Reduction of Conjugated Carbonyl Compounds with NaBH<sub>4</sub>/Wet TiO<sub>2</sub> System under Solvent-Free, Solid-Gel and Microwave Irradiation

Entry	Substrate	Product	Solvent-free and solid-gel			Microwave irradiation <sup>d</sup>					
			Method <sup>a</sup>	Molar ratio NaBH <sub>4</sub> /Subs.	Condition <sup>b</sup>	Time/min	Yield/% <sup>c</sup>	Molar ratio NaBH <sub>4</sub> /Subs.	Wet %	Time/sec	Yield/% <sup>c</sup>
1			(A)	1:1	RT	15	95	0.5:1	40	20	95
			(B)	0.5:1	RT	5	96				
2			(A)	2:1	Oil bath	60	70	2:1	100	120	94
			(B)	2:1	RT	30	96				
3			(A)	2:1	Oil bath	60	45	2:1	100	120	90
			(B)	2:1	RT	60	98				
4			(A)	1:1	RT	15	94	0.5:1	40	20	92
			(B)	0.5:1	RT	10	90				
5			(A)	2:1	Oil bath	60	55	2:1	100	120	95
			(B)	1:1	RT	35	96				




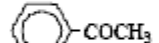

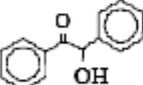

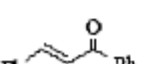
<sup>a</sup>Method A: reactions were carried out in the presence of wet TiO<sub>2</sub> (0.5 g, 20% m/m) under solvent-free condition; Method B: the reactions were carried out in the presence of wet TiO<sub>2</sub> (0.5 g, 20% m/m) and 0.5 ml of CH<sub>3</sub>CN in a solid-gel media; <sup>b</sup> the temperature of oil bath was 70-75 °C; <sup>c</sup> Yields refer to isolated pure products; <sup>d</sup> The reactions were irradiated with microwaves (300 W) in the presence of TiO<sub>2</sub> (0.5 g) at the defined wet %.

Table 4. Chemoselective Reduction of Aldehydes and Ketones with NaBH<sub>4</sub>/Wet TiO<sub>2</sub> System<sup>a</sup>

Entry	Substrate 1	Substrate 2	Molar ratio <sup>b</sup>	Time/min	Conv.1/% <sup>c</sup>	Conv.2/% <sup>c</sup>
1			1:1:1	15	100	0
2			1:1:1	15	100	0
3			1:1:1	5	85	5
4			1:1:1	15	100	0
5			1:1:1	15	100	0
6			1:1:1	15	100	0

<sup>a</sup>reactions were carried out in the presence of wet TiO<sub>2</sub> (0.5 g, 20% m/m) under solvent-free condition ; <sup>b</sup> Molar ratio as NaBH<sub>4</sub>/Substrate 1/Substrate 2; <sup>c</sup> Conversions refer to TLC monitoring and isolated pure products.

Table 5. Comparison of the Reduction of Carbonyl Compounds with NaBH<sub>4</sub>/wet TiO<sub>2</sub> and NaBH<sub>4</sub>/dry Al<sub>2</sub>O<sub>3</sub> Systems under Microwave Irradiation

Entry	Substrate	NaBH <sub>4</sub> /wet TiO <sub>2</sub> <sup>a</sup>			NaBH <sub>4</sub> /dry Al <sub>2</sub> O <sub>3</sub> <sup>14</sup>		
		Molar ratio NaBH <sub>4</sub> /Subs.	Time/sec	Yield/%	Molar ratio NaBH <sub>4</sub> /Subs.	Time/sec	Yield/%
1		0.5:1	40	98	1:1	--	93
2		0.75:1	40	97	1:1	--	90
3		0.5:1	30	98	1:1	40	87
4		2:1	120	97	1:1	30	87
5		2:1	120	95	5:1	120	92
6		2:1	120	96	8:1	180	79
7		0.5:1	20	95 <sup>b</sup>	1:1	--	90 <sup>b</sup>
8		2:1	120	90 <sup>b</sup>	8:1	--	60 <sup>b</sup> 40 <sup>c</sup>

<sup>a</sup> The present method, <sup>b</sup> 1,2-reduction; <sup>c</sup> 1,4-reduction.

different ketones was achieved perfectly with  $\text{TiO}_2$  under microwave irradiation (Table 2). The results shows that generally using 1-2 molar equivalents of  $\text{NaBH}_4$  in the presence of wet  $\text{TiO}_2$  (40-100% m/m) were the requirements for the complete reduction of ketones to their corresponding secondary alcohols in 85-97% yields. Acyloins and  $\alpha$ -diketones were also reduced to vicinal diols using 2 molar equivalents of  $\text{NaBH}_4$  in the presence of wet  $\text{TiO}_2$  (100 m/m) under microwave irradiation within 2 minutes (Table 2, entry 15-17).

The effect of microwave irradiation on the regioselective 1,2-reduction of  $\alpha,\beta$ -unsaturated carbonyl compounds was examined with the reduction of cinnamaldehyde by  $\text{NaBH}_4$ /wet  $\text{TiO}_2$  system. The reduction was carried out with 0.5 molar equivalent of  $\text{NaBH}_4$  in the presence of wet  $\text{TiO}_2$  (40% m/m) within 20 seconds (Table 3, entry 1). Cinnamyl alcohol was obtained in a perfect regioselectivity and yield. The possibility of this protocol was further examined with the 1,2-reduction of structurally different conjugated enals and enones. The reductions were accomplished by 0.5-2 molar equivalents of  $\text{NaBH}_4$  in the presence of wet  $\text{TiO}_2$  (40-100% m/m) under microwave irradiation within 1-2 min. Table 3 shows that the corresponding allylic alcohols were obtained in a perfect regioselectivity and efficiency (90-95%).

Comparison of our results with those reported by  $\text{NaBH}_4$ /dry  $\text{Al}_2\text{O}_3$ /microwave system<sup>14</sup> shows that in view points of the molar equivalents of  $\text{NaBH}_4$ , efficiency, rate and regioselectivity of reductions, our protocol is more efficient (Table 5).

The exact mechanism for the influence of water in wet  $\text{TiO}_2$  is not clear, however, we think that the following factors maybe play a role in this acceleration:

- The adsorbed water on the surface of  $\text{TiO}_2$  can solubilize  $\text{NaBH}_4$  and therefore fine dispersion of the reducing agent on the surface of  $\text{TiO}_2$  and subsequently more interaction with the substrate makes an acceleration

- $\text{TiO}_2$  in the presence of water by showing a Lewis acidity character for the carbonyl group, makes this functional group susceptible for the hydride attack

- The formation of an active new species on the surface of  $\text{TiO}_2$  as Titanato-borohydride maybe promote the reduction.

- Hydrolysis of the generated alkoxy-borate intermediate by the adsorbed water on the surface of  $\text{TiO}_2$  exhibits an acceleration.

## CONCLUSION

In conclusion, we have shown that the presence of water on the surface of  $\text{TiO}_2$  (wet  $\text{TiO}_2$ ) effectively accelerates reduction of carbonyl compounds with  $\text{NaBH}_4$  under solvent-free, solid-gel and microwave irradiation. At solvent-free condition reduction of aldehydes with  $\text{NaBH}_4$ /wet  $\text{TiO}_2$  system was taken place fast and efficiently at room temperature, however, reduction of ketones was accomplished with low-moderate yields of products at 70-75 °C. Aliphatic ketones showed higher efficiency at room temperature. In a solid-gel media reduction of carbonyl compounds was extremely accelerated using lower amounts of  $\text{NaBH}_4$ . The solvent-free reduction of carbonyl compounds by  $\text{NaBH}_4$ /wet  $\text{TiO}_2$  system was investigated successfully under microwave irradiation (300 W). In the case of conjugated carbonyl compounds, the reductions were accomplished by  $\text{NaBH}_4$ /wet  $\text{TiO}_2$  with excellent regioselectivity and efficiency under solvent-free, solid-gel and microwave irradiation. We think that in view points of high efficiency, chemo- and regioselectivity of the reductions as well as the benefits of solid state reactions,  $\text{NaBH}_4$ /wet  $\text{TiO}_2$  system could be a synthetically useful method for the reduction of carbonyl compounds.

## ACKNOWLEDGMENTS

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