

Chemoselective Reduction of Carbonyl Compounds Corresponds to Alcohols by Sodium Borohydride Adsorbed in Silica Lipid Substrate as a Novel Chemical Agent

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Abstract: Selective reduction of carbonyl functional group in the presence of other unsaturated group is an often synthetic problem; serious attempts were established to solve the problem. In this research, a newly synthesized reagent; sodium borohydride adsorbed in silica lipid substrate was developed. The new adsorbent was selective for the reduction of aldehydes in presence of ketones; also it had selectively reduction properties between some aldehydes. Sodium borohydride adsorbed in silica lipid substrate as a novel chemical agent was readily prepared in high yield and in stable condition. In this work, effect of some experimental conditions; such as solvent, temperature, molar ratio of chemical reagents on efficiency and reaction yield was defined through IR and ¹H-NMR spectroscopes. From the experimental data, it was found that the novel reducing agent at optimum condition had a wide range of aldehydes reduced to the corresponding alcohol in presence of ketones. The chemoselective procedure under the moderate reaction condition was fast and efficient which was resulted in excellent yields.

Key words: Carbonyl Compounds • Chemoselective reduction • NaBH₄ • Silica lipid substrate • Aldehydes • Ketones

INTRODUCTION

Reduction is one of the frequently used reactions in organic synthesis. For such purposes, a vast variety of reducing agents have been introduced in the literature [1]. Chemo, stereo and regioselective reductions of carbonyl compounds correspond to alcohols are some of the important functional group conversations in organic synthesis [2-3]. A variety of reagents, namely poly methyl hydro siloxan (PMHS) [5-6], Sodium dithionate [7] and nickel boride have been employed to perform this transformation [8].

Among the powerful and mild reducing agents have been developed for the reduction of functional groups, LiAlH₄ and NaBH₄ are the most commonly used reagents in the synthesis of organic compounds [9-10]. Lithium aluminum hydride is an exceedingly powerful reducing agent which is practically capable of reducing all-organic functional groups [11-13]. Consequently, it is quite difficult to apply such reagent for the selective reduction

of multifunctional molecules. On the other hand, NaBH₄ is a mild reducing agent which reduces only aldehydes, ketones and acyl chloride functional groups. In past few decades, enhancement of selectivity and efficiency of the well developed reducing agents continued to be a nodal point to diverse and considerable efforts have been made to modify these two extremes [14-17].

However, modification of the reducing power of NaBH₄, has been realized by: (i) substitution of the hydride(s) with other groups; this may exert marked strict and electronic influences upon the reactivity of the substituted complex ion, (ii) variation in the alkali metal cation and metal cation in the complex hydride, (iii) concurrent cation and hydride exchange, (iv) use of ligands to alter behavior of the metal hydrides, (v) combination of borohydride with metal, metal salts, Lewis acids, mixed solvent systems or some other agents, (vi) change of the cation to quaternary and phosphonium borohydrides and finally (vii) use of polymers and solid beds for supporting the hydride species [19].

Polymer supported reagents have gained in popularity in last two decades. These reagents have been found wide application in organic and inorganic synthesis [20]. However, silica lipid substrate as Polymer Supported reagents was first reported in 1985. The reagent has been used in hydrophobic matrix for proteins immobilization [21]. Furthermore, to the best of our knowledge there is no report on precipitation of NaBH_4 on silica lipid substrate to evaluate the efficiency, chemo selectivity and feasibility of traditional reducing agent in organic synthesis.

The purpose of present work is to investigate on sodium borohydride adsorbed in silica lipid substrate. The adsorbent showed high selectivity in the reduction of carbonyl compounds in THF medium. Frequently, selective reduction of a carbonyl group in presence of other unsaturated functional groups is a synthetic problem. In recent years, a lot of procedures have been developed to overcome the stated disadvantages [22-24]. However, in this investigation effect of some experimental parameters such solvent, temperature, molar ratio of reagents on efficiency and percentage of reaction yield was evaluated and the optimum condition was proposed.

MATERIALS AND METHODS

Materials and Apparatus: All chemical and solvents (aldehydes, ketones, THF, NaBH_4 and silica lipid) were supplied by Merck (Darmstadt, Germany). The reactions were monitored by TLC using silica gel plates. The products were purified by flash chromatography on silica gel (Merck; 230-400 mesh). The purity of products were identified by comparison of their IR and ^1H -NMR spectra and physical data with those of authentic samples. ^1H -NMR spectrum was measured at 90 MHz with a JEOL JNM-EX90 spectrometer using TMS as an internal reference and $\text{DMSO}-d_6$ solvent. Also, IR spectra were recorded with a Perkin-Elmer spectrum instrument.

Preparation of NaBH_4 Adsorbed in Silica Lipid Substrate: In order to prepare NaBH_4 adsorbed in silica lipid substrate, 3.8 g of sodium borohydride and 50 g of silica lipids in 100 ml THF were mixed for 15 min on a mild magnetic stirrer and immediately the solvent was evaporated with rotary operator to prepare pure powder product as polymer supported reagents.

Reduction of Aldehydes and Ketones: In order to prepare reaction solution, a specified volume stock solution of target compounds (aldehydes or ketones) and substrate (NaBH_4 adsorbed in silica lipid) were added in a volumetric flask and the flask was filled with tetrahydrofuran (THF)

as a suitable solvent. In a representative trial, in a round-bottom flask equipped with a magnetic stirrer, 5 mmol of the target reagent (aldehydes or ketones), 5 mmol NaBH_4 adsorbed in silica lipid substrate (section 2.2) and 25 ml tetrahydrofuran (THF) as solvent were added in a 100 ml volumetric flask and then the mixture was stirred 2-120 and 5-10 hrs for aldehydes and ketones, respectively. Subsequently, the reaction followed up by TLC ($\text{EtOAc}-\text{CCL}_4$ 4:1) and after a period of mixing and ending of the oxidation process, the experiment was finished and the solid product was separated through a short pad of silica gel and washed by THF (10 ml). Finally, the solvent was evaporated in a rotary operator to gain pure powder product. If necessary, the crude product was purified by column chromatography on silica gel using a mixture of ethyl acetate and carbon tetrachloride as eluent agent (4:1). However all products were analyzed by IR and ^1H -NMR spectroscopy techniques and the results summarized in Tables 1-3.

RESULTS AND DISCUSSION

Preparation of Polymer Supported Reagents: As mentioned in experimental section, sodium borohydride adsorbed in silica lipid substrate was readily prepared at high yield by addition of silica gel lipid into the solution of NaBH_4 and THF during 15 minutes at room temperature. However, as illustrated in Figure 1, filtration and drying of the precipitate powder resulted in a white powder with the Si-O-R groups. The introduced polymer supported reagent is non-hygroscopic and could be stored in a glass and polyethylene bag for long periods of time without any decomposition.

Effect of Solvent on the Reduction Reaction: The solvent effect on the reduction of unsaturated carbonyl compounds was evaluated in different solvents. The reduction of benzaldehyde with sodium borohydride adsorbed on silica lipid was evaluated with tetrahydrofuran, dioxane, dichloromethane, acetonitrile, chloroform and diethyl ether at room temperature. The results are summarized in Table 1.

The obtained data indicated that (Table 1), 1:1 molar ratio of benzaldehyde and sodium borohydride adsorbed in silica lipid substrate in THF and dioxane solvents gave excellent yield of benzyl alcohol (entry 1 and 6). However, because of convenient and safe issues requirements, THF was chosen as a suitable solvent for further reduction experiments. Effect of temperature on the reaction was also studied by carrying out the reduction of benzaldehyde at low temperature but long reaction time

Table 1: Effect of different solvents on the reduction of benzaldehyde with NaBH₄ adsorbed in silica lipid substrate^a

Entry	Solvent	Time (min)	^b Yield (%)
1	THF	8	85
2	CHCl ₃	120	65
3	CH ₃ CN	120	60
4	CH ₂ Cl ₂	120	65
5	C ₂ H ₅ OC ₂ H ₅	35	78
6	Dioxane	8	85

^aReactions were carried out at room temperature with substrate/reductant molar ratio (1:1). ^bYields refer to isolated productsTable 2: Reduction of aromatic aldehydes and ketones to the corresponding alcohols with NaBH₄ adsorbed in silica lipid substrate at optimum proposed condition

Entry	Substrate	Product	Time (min)	Yield (%)
1	C ₆ H ₅ CHO	C ₆ H ₅ CH ₂ OH	8	85
2	<i>p</i> -ClC ₆ H ₄ CHO	<i>p</i> -ClC ₆ H ₄ CH ₂ OH	5	90
3	<i>p</i> -BrC ₆ H ₄ CHO	<i>p</i> -BrC ₆ H ₄ CH ₂ OH	5	87
4	<i>o</i> -NO ₂ C ₆ H ₄ CHO	<i>o</i> -NO ₂ C ₆ H ₄ CH ₂ OH	2	82
5	<i>m</i> -ClC ₆ H ₄ CHO	<i>m</i> -ClC ₆ H ₄ CH ₂ OH	3	87
6	<i>o</i> -OHC ₆ H ₄ CHO	<i>o</i> -OHC ₆ H ₄ CH ₂ OH	25	75
7	<i>m</i> -OHC ₆ H ₄ CHO	<i>m</i> -OHC ₆ H ₄ CH ₂ OH	12	80
8	<i>p</i> -OHC ₆ H ₄ CHO	<i>p</i> -OHC ₆ H ₄ CH ₂ OH	70	65
9	<i>p</i> -MeC ₆ H ₄ CHO	<i>p</i> -MeC ₆ H ₄ CH ₂ OH	30	89
10	<i>p</i> -Me ₂ NC ₆ H ₄ CHO	<i>p</i> -Me ₂ NC ₆ H ₄ CH ₂ OH	120	75
11	C ₆ H ₅ COCH ₃	C ₆ H ₅ CHOHCH ₃	420	85
12	C ₆ H ₅ COC ₆ H ₅	C ₆ H ₅ CHOHC ₆ H ₅	330	80
13	<i>p</i> -ClC ₆ H ₄ COC ₆ H ₅	<i>p</i> -ClC ₆ H ₄ CHOHC ₆ H ₅	300	75
14	<i>p</i> -MeC ₆ H ₄ COCH ₃	<i>p</i> -OMeC ₆ H ₄ COCH ₃	500	72
15	C ₆ H ₅ CH ₂ COCH ₃	C ₆ H ₅ CH ₂ CHOHCH ₃	560	78
16	C ₆ H ₅ CH=CHCHO	C ₆ H ₅ CH=CHCH ₂ OH	20	86
17	C ₆ H ₅ CH=CHCOCH ₃	C ₆ H ₅ CH=CHCHOHCH ₃	120	80

Reactions were carried out at the optimum proposed condition. (substrate/reductant molar ratio (1:1) and room temperature)

Table 3: Reduction of selected aldehydes in the presence of aldehydes or ketones with NaBH₄ adsorbed in silica lipid substrate in THF at room temperature

Entry	Substrate	Product	Time (min)	Yield (%)
1	C ₆ H ₅ CHO	C ₆ H ₅ CH ₂ OH	11	82
	C ₆ H ₅ COCH ₃	C ₆ H ₅ COCH ₃		-
2	<i>p</i> -BrC ₆ H ₄ CHO	<i>p</i> -BrC ₆ H ₄ CH ₂ OH	15	87
	C ₆ H ₅ CH ₂ COCH ₃	C ₆ H ₅ CH ₂ COCH ₃		-
3	<i>o</i> -NO ₂ C ₆ H ₄ CHO	<i>o</i> -NO ₂ C ₆ H ₄ CH ₂ OH	7	80
	<i>p</i> -MeC ₆ H ₄ CHO	<i>p</i> -MeC ₆ H ₄ CHO		-
4	<i>p</i> -ClC ₆ H ₄ CHO	<i>p</i> -ClC ₆ H ₄ CH ₂ OH	8	87
	<i>p</i> -OHC ₆ H ₄ CHO	<i>p</i> -OHC ₆ H ₄ CHO		-
5	<i>m</i> -ClC ₆ H ₄ CHO	<i>m</i> -ClC ₆ H ₄ CH ₂ OH	8	85
	C ₆ H ₅ COC ₆ H ₅	C ₆ H ₅ COC ₆ H ₅		-
6	<i>m</i> -OHC ₆ H ₄ CHO	<i>m</i> -OHC ₆ H ₄ CH ₂ OH	15	76
	C ₆ H ₅ CH ₂ COCH ₃	C ₆ H ₅ CH ₂ COCH ₃		-
7	<i>p</i> -MeC ₆ H ₄ CHO	<i>p</i> -MeC ₆ H ₄ CH ₂ OH	45	85
	<i>p</i> -OMeC ₆ H ₄ COCH ₃	<i>p</i> -OMeC ₆ H ₄ COCH ₃		-

Reactions were carried out at optimum proposed condition (substrate/reductant molar ratio (1:1) and room temperature)

was required to achieve complete conversion to benzyl alcohol. Therefore, tetrahydrofuran (THF) was chosen as suitable solvent for reduction of the unsaturated carbonyl compounds at room temperature.

Chemo-Selectivity of the Reduction Reactions: In order to evaluate the applicability of the proposed method for the reduction of aromatic aldehydes and ketones to corresponding alcohols, a numbers of aromatic aldehydes

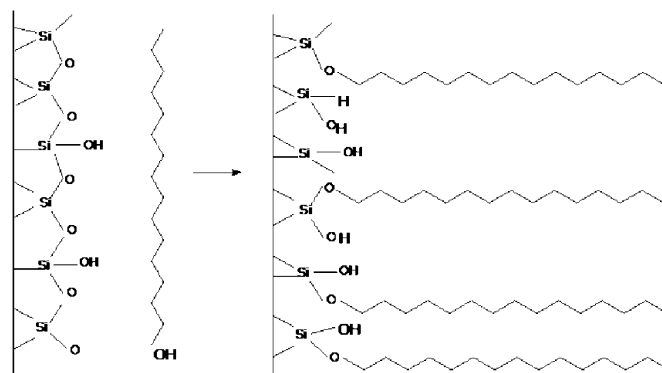


Fig. 1: Chemical structural of investigated silica supported reagent based on sodium borohydride adsorbed in silica lipid substrate

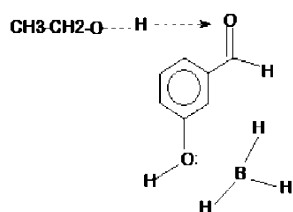


Fig. 2: Induced electronic effect of Hydroxyl group at meta position of 3-hydroxy-benzaldehyde.

and ketones were treated at optimum reduction and the proposed condition. The obtained results are summarized in Tables 2 and 3. Based on illustrated results (Table 2), it is obvious that some aromatic substrates, such as: benzaldehyde, 2-nitro-benzaldehyde and 3-chloro-benzaldehyde were rapidly converted to the corresponding alcohol. Under the moderate reaction conditions, excellent reaction yields were obtained (Table 2, entries, 1-5).

However, as it was expected the presence of some electron acceptor groups such as Cl, Br and N in the aldehydes, decreased the electron density and subsequently increased the nucleophilic property of carbonyl centers forced the nucleophilic attacked by hydride ion and consequently the rate of reduction reaction has increased.

Conversely in the case of aromatic ketones, presence of electron acceptor functional groups such as Cl, Br and N groups do not have any positive effect on reduction reaction but also a reduction difficulty was observed with NaBH_4 adsorbed in silica lipid substrate at room temperature (Table 2, Entries, 11, 12, 13, 14 and 15).

It is noteworthy that, unlike other reduction hydrolytic method, the major drawback of over reduction of the resulting alcohol was not observed under reactions. The α , β -unsaturated derivatives were very efficiently

reduced without any further effect on olefinic bond and the reaction is essentially chemoselective (Table 2, Entries 16, 17).

On the other hand, presences of some electron donor groups such as alkyl and hydroxyl in the aldehydes structure consequence to increases in the electron density of the carbonyl group and decreasing in the rate of reduction reaction. Exceptions were observed in 3-hydroxy-benzaldehyde compound with electron donor groups at meta position which has higher rate of reduction reaction respect to 4-hydroxy-benzaldehyde, 4-methoxy benzaldehyde and 4-methyl benzaldehyde.

As illustrated in Figure 2, it may be related to induce electronic effects of hydroxyl group at meta position against resonance effects. Also 3-hydroxy-benzaldehyde by form ester borate and transfer the hydride ion through intermolecular manner forced the reduction reaction.

According to the result of Table 2, the similar trend can be observed in the reduction reaction of ketones to the corresponding alcohol. However, the steric and electronic effects in the reduction of ketones by this reagent, affected the efficiency of the procedure. For examples, presence of an electron donor group at position 4 reduces the activity of 4-methoxy-acetophenone respect to acetophenone. On the other hand, presence of electron acceptor group such as Cl, can forced the reduction reaction.

The summarized results in Table 3 has interesting point to mention that sodium borohydride adsorbed in silica lipid substrate selectively reduced aldehydes to corresponding alcohol in the presence of ketones in THF at room temperature. An equimolar mixture of aldehyde and ketone was treated with the proposed novel reagent, only aldehyde was reduced, while the ketone remained as unreacted compound.

CONCLUSION

In summary, a convenient, fast, efficient and novel chemoselective method for the reduction of different aldehydes to the corresponding alcohol through a polymer supported reagents procedure was developed. In a convenient and simple procedure, sodium borohydride (NaBH_4) adsorbed in silica lipid substrate, for the selective reduction of aldehydes in presence of ketones and some aldehydes was prepared. However, the synthesized reagent has desired physical, chemical and performance properties. In presence of synthesized reagent at optimum proposed condition, number of aromatic α , β -unsaturated aldehydes and ketones were reduced to the corresponding alcohols without reducing the C=C double bonds. Finally, the novel introduced method has significant advantages over traditional reduction procedures such as selectivity, appropriate conversion rate and high yields at mild reaction condition.

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