

NaBH₄/NaHSO₄·H₂O a Heterogeneous Acidic System for a Mild and Convenient Reduction of Carbonyl Compounds under Protic Condition

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Z. Naturforsch. **60b**, 453 – 457 (2005); received October 21, 2004

NaBH₄ in the presence of sodium bisulfate (NaHSO₄·H₂O), a weakly acidic reagent, efficiently reduces a variety of carbonyl compounds such as aldehydes, ketones, α,β -unsaturated aldehydes and ketones, α -diketones and acyloins to their corresponding alcohols in acetonitrile under heterogeneous condition. Reduction reactions were accomplished at room temperature or under reflux condition.

Key words: Borohydride Reduction, Sodium Bisulfate, Carbonyl Compounds

Introduction

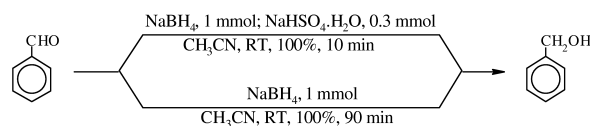
During the past decades, sodium borohydride as a key reagent has played an important role in the reduction of organofunctional groups in modern organic synthesis [1]. This reagent is a relatively mild reducing agent and mostly used for the reduction of aldehydes and ketones in protic solvents. In order to control the reducing power of NaBH₄, hundreds of substituted boron hydrides have been made and introduced in chemical literature and many of them are now commercially available. In fact, advances in this field have been realized by: a) substitution of the hydride(s) with other substituents which may exert marked steric or electronic influences upon the reactivity of substituted complex ion [2], b) variation of metal cation in the hydride complex [3], c) a concurrent cation and hydride exchange [4], d) use of amino or phosphino ligands to alter behavior of the metal hydroborates [5], e) combination of tetrahydroborates with Lewis acids, additives and mixed solvent systems [6], f) changing the cation to quaternary ammonium and phosphonium tetrahydroborates [7], g) use of polymers or solid supports for supporting the hydride species [8]. In this context, we have extensively reviewed the preparations and applications of modified hydroborate agents in organic synthesis [5c, d, 9].

In the line of outlined strategies and our literature review about the different kinds of combination systems of NaBH₄ with additives for the reduction of functional groups [6, 9], we realized that for the use of this reducing agent in the presence of an acidic catalyst or reagent, as far as we know, there is no report.

So, this subject and our continuous efforts for the introduction of modified hydroborate agents in organic synthesis [5b–g, 10] encouraged us to investigate this kind of combination system. Herein, we report for the first that time sodium borohydride in the presence of sodium bisulfate, a weakly acidic reagent, can reduce efficiently a variety of carbonyl compounds such as aldehydes, ketones, conjugated carbonyl compounds, α -diketones and acyloins to their corresponding alcohols in acetonitrile under heterogeneous condition at room temperature or reflux.

Results and Discussion

Preliminary experiments showed that reduction of benzaldehyde as a model compound took place with one molar equivalent of NaBH₄ in acetonitrile (the optimal aprotic solvent) within 90 minutes at room temperature. By adding 0.3 molar equivalents of NaHSO₄·H₂O to the mentioned reaction, the reduction reaction was accelerated dramatically and completed within 10 minutes (Scheme 1). It is notable that due to the low solubility of sodium bisulfate in acetonitrile, the reaction takes place under heterogeneous conditions. This acceleration prompted us to investigate the influence of this weakly acidic reagent and the optimum reaction conditions for the reduction of alde-



Scheme 1.

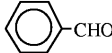
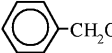
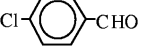
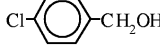
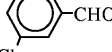
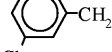
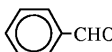
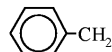
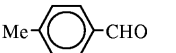
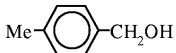
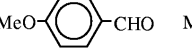
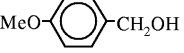
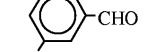
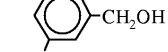
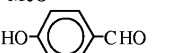
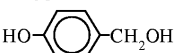
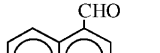
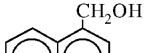
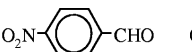
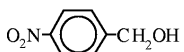
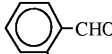
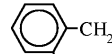
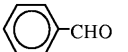
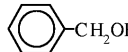
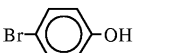
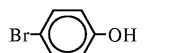
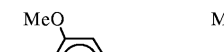

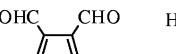
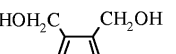
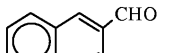
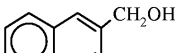


Entry	Substrate	Product	Molar ratio Subs./NaBH ₄ /NaHSO ₄	Time [min]	Yield [%] ^b
1			1:1:0.3	10	94
2			1:0.7:0.3	7	99
3			1:0.5:0.3	3	96
4			1:0.5:0.3	1	95
5			1:1:0.3	20	97
6			1:1:0.3	15	97
7			1:1:0.3	6	94
8			1:2:0.4	6	95
9			1:1:0.3	10	99
10			1:0.5:0.2	2	93
11			1:0.5:0.2	5	92
12			1:0.7:0.3	2	98
13			1:0.7:0.3	2	95
14			1:1:0.4	25	97
15			1:0.7:0.3	5	97
16			1:0.5:0.2	1	94
17			1:1:0.3	18	93

Table 1. Reduction of aldehydes to their alcohols with NaBH₄/NaHSO₄·H₂O^a.

^a All reactions were carried out in CH₃CN (3 ml) at room temperature; ^b yields refer to isolated pure products.

hydes. The results showed that generally the use of 0.5–1 and 0.2–0.4 molar equivalents of NaBH₄ and NaHSO₄·H₂O, respectively, was sufficient for the reduction of different aliphatic and aromatic aldehydes in acetonitrile at room temperature.

The corresponding primary alcohols were obtained in high to excellent yields, and the results of these reductions are summarized in Table 1. In the next attempt, we turned our attention to the reduction of ketones with this reducing system. Because of the inher-



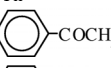
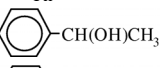
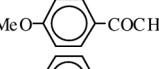
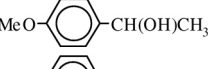
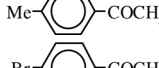
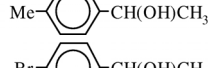
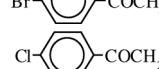
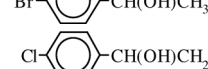
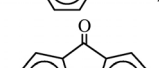
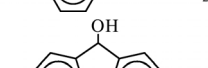
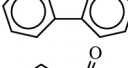
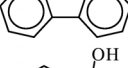






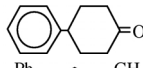
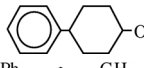
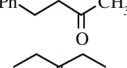
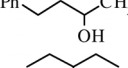


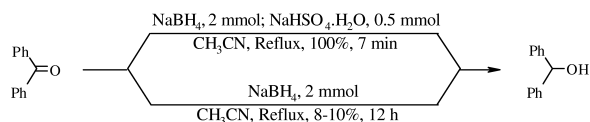
Entry	Substrate	Product	Molar ratio Subs./NaBH ₄ /NaHSO ₄	Time [min]	Yield [%] ^b
1			1:2:0.5	7	99
2			1:2:0.7	45	95
3			1:2:0.7	27	98
4			1:2:0.7	20	96
5			1:2:0.3	15	96
6			1:2:0.5	20	97
7			1:2:0.5	18	94
8			1:2:0.5	20	97
9			1:2:0.5	25	96
10			1:2:0.3	5	92
11			1:2:0.2	6	94
12			1:2:0.3	6	95
13			1:2:0.3	5	91

Table 2. Reduction of ketones to their alcohols with NaBH₄/NaHSO₄·H₂O^a.

^a All reactions were carried out in CH₃CN (3 ml) under the defined condition; ^b yields refer to isolated pure products.

ently lower reactivity of ketones relative to aldehydes, these reductions took place under forcing conditions. Reduction of different aliphatic and aromatic ketones by using 2 and 0.3–0.7 molar equivalents of sodium borohydride and sodium bisulfate, respectively, were carried out in acetonitrile under reflux. The reductions were completed within 5–45 minutes and the corresponding secondary alcohols were obtained in high to excellent yields (91–99%). The results of these reductions are summarized in Table 2.

To clarify the effect and influence of sodium bisulfate in the reduction of ketones, we performed the reduction of benzophenone as a model compound with 2 molar equivalents of NaBH₄ under reflux condition



Scheme 2.

for 12 hours without using NaHSO₄·H₂O. The results showed that in this case we had only 8–10% conversion. When the reaction was performed in the presence of 0.5 molar equivalents of NaHSO₄·H₂O, it was completed in 7 minutes and the corresponding benzhydrol was obtained in 99% yield (Scheme 2).

The reduction of α -diketones and acyloin compounds with NaBH₄/NaHSO₄·H₂O system was also examined. Reduction of α -diketones with 2:0.5 molar equivalents of NaBH₄/NaHSO₄·H₂O to give the corresponding vicinal diols was carried out efficiently in acetonitrile under reflux condition. The reactions were completed within 6–8 minutes (Table 3). All attempts to reduce α -diketones to acyloin compounds were unsatisfactory and only vicinal diols were obtained from the reactions. Reduction of acyloin compounds was also achieved easily and efficiently with this reducing system under the defined conditions (Table 3).

Allyl alcohols are important synthetic materials and their preparation from the regioselective 1,2-reduction

Entry	Substrate	Product	Molar ratio Subs./NaBH ₄ /NaHSO ₄	Time [min]	Yield [%] ^b
1			1:2:0.5	6	97
2			1:2:0.5	4	98
3			1:2:0.5	8	98
4			1:2:0.5	5	99
5			1:2:0.5	7	93
6			1:2:0.5	4	96
7			1:2:0.5	7	95

Table 3. Reduction of α -diketones and acyloins with NaBH₄/NaHSO₄·H₂O^a.

^a All reactions were carried out in CH₃CN (3 ml) under reflux condition; ^b yields refer to isolated pure products.

Entry	Substrate	Product	Molar ratio Subs./NaBH ₄ /NaHSO ₄	Condition	Ratio 1,2:1,4	Time [min]	Yield [%] ^b
1			1:1:0.3	RT	100:0	2	97
2			1:2:0.5	Reflux	100:0	6	97
3			1:2:0.7	Reflux	100:0	13	98
4			1:1:0.3	RT	100:0	25	92
5			1:2:0.7	Reflux	100:0	12	98

Table 4. Reduction of conjugated carbonyl compounds with NaBH₄/NaHSO₄·H₂O^a.

^a All reactions were carried out in CH₃CN (3 ml) under the defined condition; ^b yields refer to isolated pure products.

of α,β -unsaturated aldehydes and ketones is a widely utilized method in organic synthesis. Considerable efforts have been made in the development of various hydride transferring agents for this purpose [1]. In this context, we decided to evaluate the ability of the combination system of NaBH₄ and NaHSO₄·H₂O for the regioselective 1,2-reduction of conjugated carbonyl compounds. We observed that reduction of cinnamaldehyde as a model compound occurred exclusively as a 1,2-reduction with 1:0.3 molar equivalents of NaBH₄/NaHSO₄·H₂O in acetonitrile at room temperature. The reduction was completed within 2 minutes with an excellent yield of cinnamyl alcohol (97%). Reduction of citral was also achieved with this reducing system and geraniol was obtained in high yields. The reduction of conjugated ketones such as benzalacetone, benzalacetophenone and β -ionone were also carried out effectively with 2:0.5 molar equivalents of NaBH₄/NaHSO₄·H₂O under reflux condition. The corresponding secondary allylic alcohols were obtained in excellent yields and regioselectivity (Table 4).

The mechanism for the influence of NaHSO₄ is not clear, but we think that the following pathways may play a key role in these accelerations: a) sodium bisulfate heterogeneously protonates the carbonyl group which make it more susceptible for the hydride attack, b) this weakly acidic reagent heterogeneously catalyzes the decomposition of the borohydride moiety with the liberation of active molecular hydrogen which reduces the carbonyl group, since in all reactions we observed the gentle generation of hydrogen gas throughout the reduction.

In conclusion, we have shown that reduction of a variety of carbonyl compounds with NaBH₄ was accelerated dramatically in the presence of weakly acidic NaHSO₄·H₂O in acetonitrile. The reactions were accomplished under heterogeneous conditions. Reduction of aldehydes was performed at room temperature and that of ketones under reflux condition. The regioselective reduction of α,β -unsaturated aldehydes and ketones was achieved in exclusive 1,2-reduction manner. The ability of this reducing system was fur-

ther investigated with the reduction of α -diketones and acyloin compounds to their corresponding vicinal diols. Therefore we think that these advantages as well as high to excellent efficiency of the reductions could make this procedure a synthetically useful addition to the present methodologies.

Experimental Section

General

All substrates and reagents were obtained from commercially sources with highest quality and used without further purification. The products were characterized by a comparison with authentic samples (melting or boiling points) and their ¹H NMR or IR spectra. Organic layers were dried with anhydrous sodium sulfate before concentration *in vacuo*. All yields refer to isolated pure products. TLC was applied for the purity determination of substrates or products and reaction monitoring on silica gel PolyGram SILG/UV-254 plates.

Reduction of carbonyl compounds to their alcohols with the NaBH₄/NaHSO₄·H₂O system; typical procedure

To a round-bottomed flask (10 ml) equipped with magnetic stirrer and charged with the solution of benzaldehyde (0.106 g, 1 mmol) in CH₃CN (3 ml), NaHSO₄·H₂O (0.041 g, 0.3 mmol) and then NaBH₄ (0.038 g, 1 mmol) was added. The resulting mixture was stirred magnetically at room temperature for 10 min. TLC monitored the progress of reaction (eluent CCl₄/Et₂O (5:2)). After completion of the reaction, distilled water (3 ml) was added to the reaction mixture which was stirred for an additional 5 min. The mixture was extracted with CH₂Cl₂ (3 × 8 ml) and dried over anhydrous sodium sulfate. Evaporation of the solvent and short column chromatography of the resulting crude material over silica gel (eluent CCl₄/Et₂O (5:2)) afforded the pure liquid benzyl alcohol (0.102 g, 94% yield, Table 1).

Acknowledgements

The authors gratefully acknowledge the financial support of this work by the research council of Urmia University.

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