

Ultrasound-Promoted Reduction of Conjugated Enones, α -Diketones and Acyloins with NaBH_4 under Aprotic Condition

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Z. Naturforsch. **59b**, 699 – 703 (2004); received December 28, 2003

A variety of conjugated enones are reduced regioselectively to their corresponding allylic alcohols with NaBH_4 under ultrasound irradiation. Reduction reactions were performed in THF at room temperature and the product alcohols were obtained in high to excellent yields. This system is also efficient for the reduction of α -diketones and acyloins to vicinal diols.

Key words: Ultrasound, Borohydride Reduction, Conjugated Enones, α -Diketones, Acyloins

Introduction

Regioselective 1,2-reduction of α,β -unsaturated aldehydes and ketones with metal hydride reducing agents due to competing 1,2- vs. 1,4-attack by hydride is often difficult to achieve in organic synthesis [1]. In spite of the substantial evidence, the tendency for sodium borohydride to reduce enones in a conjugate sense is highly solvent-dependent [2] and often ignored, but the requirement for reduction to corresponding allylic alcohols has led to the development of several new specific reagents. Among the various reducing systems which have been developed for 1,2-reduction of conjugated enones, the reagents such as diisobutylaluminum hydride (DIBAL-H) [3], triisobutylaluminum (TIBAL) [4], lithium aluminum hydride [2a], 9-borabicyclo[3.3.1]nonane (9-BBN) [5], lithium *n*-butylborohydride [6] and sodium borohydride in the presence of lanthanides [7] and calcium chloride [8] are generally the most efficient and convenient.

Nowadays, acceleration of reactions by using ultrasound irradiation is an interesting strategy in organic synthesis: numerous reviews and papers have demonstrated its importance [9]. Sonic condition not only accelerates chemical reactions but also it reduces the number of steps which are required using normal conditions, cruder reagents can be used and reactions can be initiated without any additives. The chemical effects of ultrasound are due to the phenomena of acoustic cavitations [9d] and the primary chemical reactions result from a transient state of higher temperatures and pressures [10].

Results and Discussion

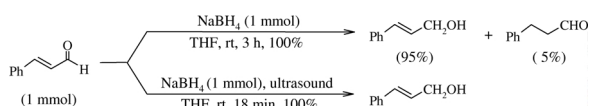
Reduction of conjugated enones: Selective 1,2-reduction of α,β -unsaturated carbonyl compounds is usually achieved by using modified hydroborate agents which are formed: a) by the replacement of hydride(s) with sterically bulky substituents or electron-withdrawing/releasing groups in order to discriminate between the structural and electronic environments of the carbonyl groups [2c, 5, 6, 11], b) combination with Lewis acids [7, 8] and mixed solvent systems [2a–c, 11e], c) using of transition metal hydroborates and its new modifications [12, 13] d) use of quaternary ammonium [14] and phosphonium tetrahydroborates [15], and e) immobilization on an anionic exchange resin [16].

As far as we know, the application of ultrasound in regioselective 1,2-reduction of conjugated enones has not been reported yet. Therefore, in the line of outlined strategies and ongoing attention to preparation and application of modified hydroborate agents [12, 17] in organic synthesis, we decided to evaluate the influence of ultrasound irradiation in reduction of conjugated enones with commercially available sodium borohydride under aprotic conditions. Our preliminary observations reveal that when cinnamaldehyde as a model compound is reduced with NaBH_4 in THF, the selectivity ratio of 1,2- vs. 1,4-reduction is 95:5 at room temperature within 3 h, whereas this reaction under sonication shows a perfect selectivity for 1,2-reduction in shorter reaction time (Scheme 1).

Table 1. Reduction of conjugated enones with NaBH_4 -ultrasound system^a.

Entry	Substrate	Product	Molar ratio NaBH_4 /Substrate	Ratio 1,2:1,4	Time (h)	Yield (%) ^b	M.p. or B.p. (°C) found calcd.
1			1:1	100:0	0.3	96	34–35 33–35 [21a]
2			1:1	100:0	0.92	97	33–34 33–34 [21b,c]
3			1:1	100:0	0.83	98	56–57 55–57 [18d]
4			1:1	100:0	0.4	92	164–165 164–166 [21a]
5			1:1	100:0	0.32	90	– –
6			1:1	100:0	1.1	95	229–230 229–230 [21a]
7			1:1	100:0	1.33	96	107/3 107/3 [21d] (mmHg)

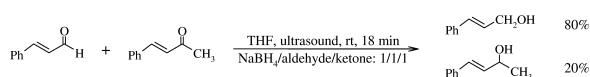
^a All reactions were performed in THF at room temperature; ^b yields refer to isolated pure products.



Scheme 1.

Accordingly, we decided to apply this procedure to other enones. We turned our attention to the reduction of benzalacetone as a conjugated ketone at the same condition. The reaction was also easily performed with an equimolar amount of NaBH_4 at room temperature. The corresponding secondary allylic alcohol was obtained regioselectively in excellent yield (Table 1, entry 2). The usefulness of this utility was demonstrated by regioselective 1,2-reduction of other enones with 1 molar equivalent of NaBH_4 under ultrasound irradiation in THF. In these cases, the observed selectivity for 1,2-reduction was also excellent and the corresponding allylic alcohols were obtained in high to excellent yields (90–99%) (Table 1).

Since aldehydes are generally more reactive than ketones, this subject encouraged us to investigate the chemoselectivity for reduction of conjugated aldehydes over ketones. Therefore, in a typical reaction we performed the competitive reduction of a mixture of an equimolar amount of cinnamaldehyde and benzalacetone with NaBH_4 under sonication. The experiment



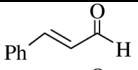
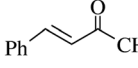
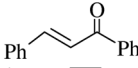
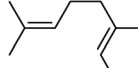
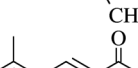
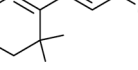
Scheme 2.

showed that the selectivity ratio for reduction of aldehyde over ketone was 80:20 within 18 min (Scheme 2).

To highlight the efficiency of the NaBH_4 -ultrasound system for the reduction of conjugated enones, we compared our results with those obtained with other reagents such as NaBH_4 [17a], $\text{NaBH}_4/\text{Dowex1-x8}$ [17a], $\text{NaBH}_3(\text{OAc})$ [2c], NaBH_3CN [11e], $\text{Li}(\text{n-BuBH}_3)$ [6], $(\text{i-PrO})_2\text{TiBH}_4$ [13a], and $(\text{Ph}_3\text{PMe})\text{BH}_4$ [15]. Investigation of the results show that with respect to efficiency and regioselectivity, our system is either more efficient or comparable (Table 2).

Reduction of α -diketones and acyloins: The synthetic utilities of vicinal diols are well known in organic synthesis and their preparation from the reduction of acyloins or α -diketones has attracted a great deal of attention. Reduction of α -diketones usually gives a mixture of α -hydroxy ketones and vicinal diols. Selective reduction of α -diketones to acyloins [18] or vicinal diols [19] can be achieved with some chemical or biochemical reagents. Reduction of α -diketones to vicinal diols with modified hydroborate agents is also a subject of interest [12,17a] and this goal is easily

Table 2. Comparison of 1,2-reduction of conjugated enones with the NaBH_4 -ultrasound system and other reported reagents.

Entry	Substrate	Molar ratio ^a , Time (h), Yield (%) and Ratio of 1,2:1,4							
		I	II [17a]	III [17a]	IV [2c]	V [11e]	VI [6]	VII [13a]	VIII [15]
1		1(0.3)(96) (100:0)	1(0.7)(96) (100:0)	1(3)(93) (95:5)	1.67(20)(70) (99:1)	2(1.5)(80) (100:0)	–	1(0.08)(90) (> 99 :< 1)	1(b)(95) (100:0)
2		1(0.92)(97) (100:0)	1(1.4)(98) (100:0)	1(2.8)(96) (95:5)	1.67(20)(70) (96:4)	2(1.5)(77) (100:0)	1(2)(98) (100:0)	1(0.08)(97) (> 99 :< 1)	1(3.5)(90) (100:0)
3		1(0.83)(98) (100:0)	1(0.7)(95) (100:0)	1(1.7)(95) (90:10)	–	3(2.5)(0)	1(2)(99) (100:0)	–	1.2(6)(90) (100:0)
4		1(1.1)(95) (100:0)	1(1.3)(94) (100:0)	1(2.8)(90) (99:1)	1.67(20)(86) (99:1)	–	–	1(0.08)(95) (< 99 :< 1)	–
5		1(1.33)(96) (100:0)	1(2.2)(91) (100:0)	1(3)(80) (95:5)	–	2(2)(88) (100:0)	1(2)(98) (100:0)	–	1(6)(71) (100:0)
6		1(0.4)(92) (100:0)	1(0.8)(89) (100:0)	1(1)(85) (80:20)	1.67(20)(32) (99:1)	–	1(2)(84) (92:8)	–	–

^I NaBH_4 /ultrasound; ^{II} NaBH_4 /Dowex1-x8; ^{III} NaBH_4 ; ^{IV} $\text{NaBH}_3(\text{OAc})$; ^V NaBH_3CN ; ^{VI} $\text{Li}(\text{n-Bu-BH}_3)$; ^{VII} $(\text{i-PrO})_2\text{TiBH}_4$; ^{VIII} $(\text{Ph}_3\text{-PMe})\text{BH}_4$; ^a Reducing agent:substrate; ^b immediate reaction.

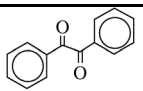
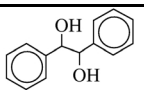
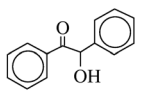
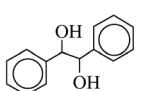
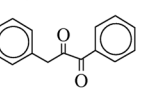
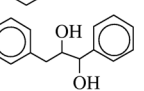
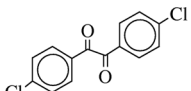
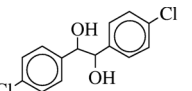
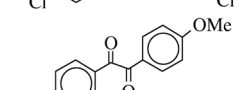
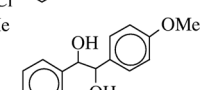
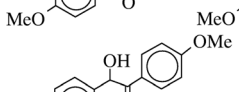
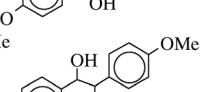
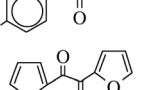
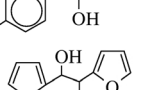
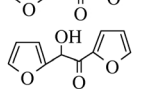
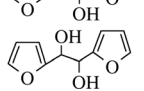
Entry	Substrate	Product	Molar ratio NaBH_4 /Substrate	Time (min)	Yield (%) ^b
1			1.2:1	12	95
2			1:1	10	98
3			1.2:1	18	96
4			1.2:1	17	96
5			1.2:1	20	98
6			1:1	14	94
7			1.2:1	12	92
8			1:1	8	95

Table 3. Reduction of α -diketones and acyloins with NaBH_4 -ultrasound system^a.

^a All reactions were performed in THF at room temperature; ^b yields refer to isolated pure products.

achieved by the NaBH_4 -ultrasound system. This system readily reduces α -diketones to their vicinal diols

in THF at room temperature and with short reaction times (12–20 min). For completion of the reactions,

1.2 molar equivalents of NaBH_4 are sufficient and the product diols are obtained in 92–98% yields (Table 3). Under different conditions, our attempts to reduce α -diketones to acyloins were unsatisfactory and only vicinal diols were identified as the sole products.

In addition, reduction of acyloins to vicinal diols is also a subject of interest in organic synthesis. The application of non-hydridic reductants [20] and modified hydroborate agents [12,17a] have been reported for such a transformation. We also found that this goal is easily achieved by the NaBH_4 -ultrasound system. The influence of ultrasound irradiation effectively accelerates reduction of benzoin to hydrobenzoin with sodium borohydride in THF. Some acyloin compounds are easily reduced to their corresponding vicinal diols in high to excellent yields with this system (Table 3).

In conclusion, we have shown that NaBH_4 in combination with ultrasound irradiation reduces a variety of conjugated enones regioselectively to their corresponding allylic alcohols in high to excellent yields and with short reaction times. Reduction reactions were performed at room temperature under aprotic condition in THF. The NaBH_4 -ultrasound system is also efficient for the reduction of acyloins or α -diketones to their corresponding vicinal diols. The cheapness and availability of the reagent, simple work-up procedure as well as the above advantages could make this procedure an attractive and synthetically useful addition to the present methodologies.

Experimental Section

Sonication was performed by using a Cole Palmer high intensity ultrasonic processor (600 W, 20 KHz) *via* a microtip probe and 30% amplitude. THF was dried prior to use by standard methods. The products were characterized by a direct comparison on TLC with authentic samples, melting/boiling points or their ^1H NMR and IR spectra. All yields refer to isolated pure products (> 97%). TLC accomplished the purity determination of the substrates, products and reactions monitoring over silica gel PolyGram SILG/UV254 plates.

Reduction of cinnamaldehyde to cinnamyl alcohol with NaBH_4 -ultrasound system, general procedure: In a round-bottom flask (10 ml) equipped with magnetic stirrer, NaBH_4 (0.037 g, 1 mmol) was added to the solution of cinnamaldehyde (0.132 g, 1 mmol) in THF (5 ml). The stirred reaction mixture was irradiated with ultrasound waves at room temperature. Sonication was continued for 18 min, and the progress of the reaction was monitored by TLC (eluent: $\text{CCl}_4/\text{Et}_2\text{O}$ (5/2)). At the end of reaction, distilled water (5 ml) was added to the reaction mixture which was stirred for additional 5 min. The mixture was extracted with CH_2Cl_2 (3×10 ml) and dried over anhydrous sodium sulfate. Evaporation of the solvent and short column chromatography of the resulting crude material over silica gel (eluent: $\text{CCl}_4/\text{Et}_2\text{O}$ (5/2)) afforded pure liquid cinnamyl alcohol (0.128 g, 96% yield, Table 1).

Acknowledgement

The authors gratefully acknowledge the Research Council of Urmia University (RCUU) for supports of this work.

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