



(Caffeine) (tetrahydroborato)zinc Complex $[\text{Zn}(\text{BH}_4)_2(\text{caf})]$: A New Stable and Efficient Reducing Agent

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ABSTRACT

In this context, (Caffeine)(tetrahydroborato)zinc complex as white stable reducing agents $[\text{Zn}(\text{BH}_4)_2(\text{caf})]$, has been prepared by complexation of one equimolar amounts of zinc tetrahydroborate and one equimolar amounts of caffeine at room temperature. Also, $[\text{Zn}(\text{BH}_4)_2(\text{caf})]$ has been used for reduce of a variety of carbonyl compounds such as aldehydes, ketones, α , β -unsaturated carbonyl compounds, acyloins and α -diketones to their corresponding alcohols in excellent yields (90-95%). The reduction reactions have been completed in appropriate times (30-90 min) by using of 0.5-1 equivalents of $[\text{Zn}(\text{BH}_4)_2(\text{caf})]$ in CH_3CN at room temperature or under reflux conditions.

Key words: $\text{Zn}(\text{BH}_4)_2$, Caffeine, Reduction, Carbonyl Compounds.

INTRODUCTION

$\text{Zn}(\text{BH}_4)_2$ is the modified borohydride agents which has better solubility in aprotic solvents, so its use and application is interesting in organic synthesis. Zinc borohydride is unique because of the coordination ability of Zn^{2+} which is imparting selectivity in hydride-transferring reactions. Zinc borohydride is moderately stable in ethereal solution and has many applications in organic synthesis¹. Zinc borohydride as a nonconventional hydride transferring agent has been reported as an efficient chemo-, regio- and

stereoselective reducing agent in several complex substrates. It can be used in a range of aprotic solvents such as, THF, Et_2O and DME². Several Combination reducing systems of $\text{Zn}(\text{BH}_4)_2$ such as $\text{Zn}(\text{BH}_4)_2/\text{TMEDA}$ ^{3a}, $\text{Zn}(\text{BH}_4)_2/\text{Me}_3\text{SiCl}$ ^{3b}, $\text{Zn}(\text{BH}_4)_2/\text{TFA}/\text{DME}$ ^{3c}, $\text{Zn}(\text{BH}_4)_2/\text{H}_2\text{O}$ ^{3d}, $\text{Zn}(\text{BH}_4)_2/\text{Al}_2\text{O}_3$ ^{3e}, $\text{Zn}(\text{BH}_4)_2/\text{C}$ ^{3f}, $\text{Zn}(\text{BH}_4)_2/2\text{NaCl}$ ^{3g}, $\text{Zn}(\text{BH}_4)_2/\text{U.S.}$ ^{3h}, and $\text{Zn}(\text{BH}_4)_2/\text{ZrCl}_4$ ³ⁱ are interesting and have been used for different reduction purposes. However, zinc tetrahydroborate has been used less than regular reducing agents in laboratory for the reduction of organic compounds, probably because of non-availability as a commercial reagent, being freshly

prepared solution just prior to use and limitation to handling and storage. So, $Zn(BH_4)_2$, has been modified as stable complexes such as $[Zn(BH_4)_2(dabco)]^4$, $[Zn(BH_4)_2(py)_n]^5$, $[Zn(BH_4)_2(PPh_3)]$ & $[Zn(BH_4)_2(PPh_3)_2]^6$, $[Zn(BH_4)_2(bpy)]^7$, $[Zn(BH_4)_2(py)]^8$, $[Zn(BH_4)_2XP_4]^9$, $[Zn(BH_4)_2(nmi)]^{10a}$ and $[Zn(BH_4)_2(nic)]^{10b}$. In continuation of our interest for preparation of new modified tetrahydroborates, we now wish to report the preparation of new stable ligand-zinc tetrahydroborate such as (caffeine) (tetrahydroborato)zinc complex, $[Zn(BH_4)_2(caf)]$ and its reducing ability in the reduction of carbonyl compounds such as aldehydes, ketones and acyloins, α -diketones to their corresponding alcohols.

RESULTS AND DISCUSSIONS

In order to determine the most appropriate reaction conditions, we first examined the reduction of benzaldehyde as a model compound as shown

in Table 1. Among the tested different solvents benzaldehyde reduction was better in CH_3CN . The optimization study showed that using 0.5 molar equivalents of $[Zn(BH_4)_2(caf)]$ in CH_3CN (3 mL) is the best conditions (Table 1, entry 9).

This procedure was also applied for the reduction of various aliphatic and aromatic aldehydes (Table 2, entries 1-9). All reductions were completed within 20-50 min by 0.5 molar equivalents of $[Zn(BH_4)_2(caf)]$ in excellent yields of products (90-95%).

Our next attempt was the reduction of ketones. We optimized the reaction conditions with acetophenone as model compound (Table 1, entries 14-18). Due to the lower reactivity of ketones relative to aldehydes, the reduction require a higher molar amounts of $[Zn(BH_4)_2(caf)]$. The reduction reactions were carried out with 1 molar equivalents of $[Zn(BH_4)_2(caf)]$ at reflux conditions in CH_3CN . All reductions were completed within 40-90 min with

Table 1: Optimization of the Reduction of Benzaldehyde and Acetophenone to their Corresponding Alcohols with $[Zn(BH_4)_2(caf)]$ at Room Temperature and Reflux Conditions

Entry	Substrate	Molar Ratio Substrate $[Zn(BH_4)_2(caf)]$	Solvent	Time/min	Conversion ^a /%
1	PhCHO	1:1	solvent free	60	100<
2	PhCHO	1:1	<i>n</i> -hexane	60	100<
3	PhCHO	1:1	$CHCl_3$	60	100<
4	PhCHO	1:1	CH_2Cl_2	60	100<
5	PhCHO	1:1	Et_2O	60	100<
6	PhCHO	1:1	DME	60	100<
7	PhCHO	1:1	CH_3CN	20	100
8	PhCHO	1:1	THF	40	100
9	PhCHO	1:0.5	CH_3CN	30	100
10	PhCHO	1:0.5	THF	60	100
11	PhCHO	1:0.25	CH_3CN	60	100<
12	PhCHO	1:0.5	CH_3OH	60	100<
13	PhCHO	1:0.5	C_2H_5OH	60	100<
14	PhCOCH ₃	1:0.5	CH_3CN	60	100<
15	PhCOCH ₃	1:1	CH_3CN	60	100<
16	PhCOCH ₃	1:2	CH_3CN	80	100
17	PhCOCH ₃	1:2	THF	160	100
18 ^b	PhCOCH ₃	1:1	CH_3CN	60	100

^a Completion of reactions was monitored by TLC (eluent; Hexane/EtOAc: 10/1), ^bThe reaction has been carried out under reflux conditions.

Table 2: Reduction of a Variety of Carbonyl Compounds such as Aldehydes (entries 1-9), Ketones (entries 10-14), α -diketones (15-16), Acyloins (entry 17) and α , β -unsaturated carbonyl Compounds (entries 18-20) to their Corresponding Alcohols with $[\text{Zn}(\text{BH}_4)_2(\text{caf})]$ as Reducing Agent in CH_3CN

Entry	Substrate	Product	Molar Ratio Substrate/ $[\text{Zn}(\text{BH}_4)_2(\text{caf})]$	Time/min	Yield ^c %
1 ^a	benzaldehyde	benzyl alcohol	1:0.5	30	91
2 ^a	4-chlorobenzaldehyde	4-chlorobenzyl alcohol	1:0.5	30	92
3 ^a	4-bromobenzaldehyde	4-bromobenzyl alcohol	1:0.5	30	95
4 ^a	2,4-dichlorobenzaldehyde	2,4-dichlorobenzyl alcohol	1:0.5	30	94
5 ^a	4-methylbenzaldehyde	4-methylbenzyl alcohol	1:0.5	40	93
6 ^a	4-methoxybenzaldehyde	4-methoxybenzyl alcohol	1:0.5	40	92
7 ^a	2-methoxybenzaldehyde	2-methoxybenzyl alcohol	1:0.5	50	94
8 ^a	3-methylbenzaldehyde	3-methylbenzyl alcohol	1:0.5	35	92
9 ^a	4-nitrobenzaldehyde	4-nitrobenzyl alcohol	1:0.5	20	90
10 ^b	acetophenone	1-phenylethanol	1:1	60	96
11 ^b	benzophenone	diphenylmethanol	1:1	90	96
12 ^b	9H-fluoren-9-one	9H-fluoren-9-ol	1:1	90	95
13 ^b	cyclohexanone	cyclohexanol	1:1	50	95
14 ^b	4-phenylcyclohexanone	4-phenylcyclohexanol	1:1	50	98
15 ^b	benzil	1,2-diphenyl ethane-1,2-diol	1:1	40	93
16 ^b	1,2-bis(4-methoxyphenyl) ethane-1,2-dione	1,2-bis(4-methoxyphenyl) ethane-1,2-diol	1:1	60	94
17 ^b	benzoin	1,2-diphenyl ethane-1,2-diol	1:1	40	92
18 ^a	cinnamaldehyde	3-phenyl-2-propen-1-ol	1:1	30	95
19 ^b	benzylideneacetone	Phenyl-3-butene-2-ol	1:1	60	95
20 ^b	chalcone	4-phenyl-3-butene-2-ol	1:1	60	96

^a The reactions have been carried out at room temperature. ^b The reactions have been carried out under reflux conditions. ^c Yields refer to isolated pure products.

Table 3: Comparison of the Reduction of Aldehydes and Ketones by $[Zn(BH_4)_2(caf)]$ in CH_3CN with other Reported Reducing Agents

Entry	Reducing Systems	Molar Ratio (Reagent./Substrate), Time/h					
		Benzaldehyde	Acetophenone	Benzophenone	Cyclohexanone	9H-fluoren-9-one	Benzoin
1	$[Zn(BH_4)_2(caf)]$	0.5, 0.5	1, 1	1, 1.5	1, 0.5	1, 1.5	1, 1
2 ⁴	$[Zn(BH_4)_2(dabco)]$	0.75, 0.7	1.2, 5.4	1.5, 8.5	-	1.5, 2.3	1, 0.17
3 ⁵	$[Zn(BH_4)_2(Ph_3P)]$	-	2, 1.25	-	2, 1	2, 0.5	-
4 ⁷	$[Zn(BH_4)_2(bpy)]$	0.25, 0.2	0.35, 0.17	1, 0.75	0.5, 0.15	1, 1.5	0.5, 0.08
5 ⁸	$[Zn(BH_4)_2(py)]$	1, 0.5	2, 2	2, 4.3	2, 2	2, 5.3	0.5, 0.5
6 ⁵	$[Zn(BH_4)_2(py)_n]$	1, 2.5	4, 30	-	4, 18	-	3, 5
7 ^{10a}	$[Zn(BH_4)_2(nmi)]$	1, <i>lm</i>	1, <i>lm</i>	-	1, 1	1.6, 18	-
8 ^{10b}	$[Zn(BH_4)_2(nic)]$	1, 0.25	2, 0.8	2, 21.5	-	-	-
9 ⁹	$[Zn(BH_4)_2XP_4]$	1, 8	2, 15	2, 48	2, 24	-	-

high to excellent yields of products (92-98%) as shown in Table 2 (entries 10-17).

We also investigated the potential of the 1,2-reduction of α,β -unsaturated aldehydes and ketones with $[Zn(BH_4)_2(caf)]$. The reduction of cinnamaldehyde with 0.5 molar equivalents of the $[Zn(BH_4)_2(caf)]$ exclusivity afforded the 1,2-reduction product after 30 min at room temperature in CH_3CN . In this reaction, cinnamyl alcohol was obtained in 95% yield (Table 2, entry 18). Under this protocol, reduction of conjugated ketones such as benzylidenacetone (Table 2, entry 19) and chalcone (Table 2, entry 20) were achieved efficiently with 1 molar equivalents of $[Zn(BH_4)_2(caf)]$ at reflux conditions in CH_3CN in excellent yields (95-96%).

The efficiency of $[Zn(BH_4)_2(caf)]$ has been compared with other reported reducing systems (Table 3). In all cases $[Zn(BH_4)_2(caf)]$ has a good potential for the reduction of organic carbonyl compounds.

The stability and shelf-life $[Zn(BH_4)_2(caf)]$ was investigated by comparing the reduction reactions of benzaldehyde as model compound under different conditions. Experiments show in adverse conditions, this reducing system is stable and reducing power remains significantly.

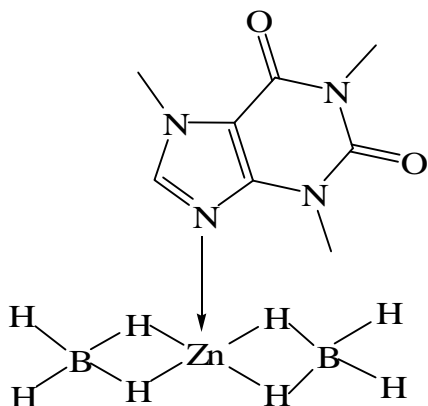
EXPERIMENTAL

All substrates and reagents were purchased from commercially sources with the best quality and used without further purification. IR and 1H NMR spectra were recorded on PerkinElmer FT-IR RXI and 300 MHz Bruker spectrometers, respectively. The products were characterized by their 1H 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. 1H NMR & TLC was applied for the purity determination of substrates, products and reaction monitoring over silica gel 60 F₂₅₄ aluminum sheet.

Preparation of (Caffeine)(tetrahydroborato)zinc Complex; $[Zn(BH_4)_2(caf)]$:

An ethereal solution of $Zn(BH_4)_2$ (0.16 M, 250 mL) was prepared from $ZnCl_2$ (5.452 g, 0.04

mol) and NaBH_4 (3.177 g, 0.084 mol) according to an available procedure in the literature [12c]. Then, caffeine (7.76 g, 0.04 mol) in ether (50 mL) was added dropwise to the ethereal solution of $\text{Zn}(\text{BH}_4)_2$ and stirred for 30 min. Evaporation of the solvent under vacuum at room temperature gave $[\text{Zn}(\text{BH}_4)_2(\text{caf})]$ as a white powder in a quantitative yield (9.16 g, 95%). Found: Zn: 22.25 %, B: 7.2 %. Calculated for $\text{C}_8\text{H}_{18}\text{B}_2\text{N}_4\text{O}_2\text{Zn}$, Zn: 22.61 %, B: 7.47%. Scheme 1.



Scheme 1: (Caffeine) (tetrahydroborate) zinc complex

Reduction of Benzaldehyde to Benzyl alcohol with $[\text{Zn}(\text{BH}_4)_2(\text{caf})]$, A Typical Procedure

In a round-bottomed flask (10 mL), equipped with a magnetic stirrer, a solution of benzaldehyde (0.106 g, 1 mmol) in CH_3CN (3 mL) was prepared. The complex reducing agent (0.144

g, 0.5 mmol) was then added as a solid and the mixture was stirred at room temperature. TLC monitored the progress of the reaction (eluent; $\text{CCl}_4/\text{Et}_2\text{O}$: 5/2). After completion of the reaction in 30 min, a solution of 5% HCl (5 mL) was added to the reaction mixture and stirred for 10 min. The mixture was extracted with CH_2Cl_2 (3×10 mL) and dried over the anhydrous sodium sulfate. Evaporation of the solvent and short column chromatography of the resulting crude material over silica gel by eluent of $\text{CCl}_4/\text{Et}_2\text{O}$: 5/2 afforded the pure liquid benzyl alcohol (0.097 g, 91% yield, table 1).

CONCLUSION

In this investigation, we have shown that $[\text{Zn}(\text{BH}_4)_2(\text{caf})]$ reduces a variety of carbonyl compounds to their corresponding alcohols in high to excellent yields. Reduction reactions were carried out with 0.5-1 molar equivalents of $[\text{Zn}(\text{BH}_4)_2(\text{caf})]$ at room temperature and reflux conditions in CH_3CN without any other additive. In addition, regioselectivity of this system was also investigated with exclusive 1,2-reduction of conjugated carbonyl compounds to their corresponding allylic alcohols in high to excellent yields. Reduction of acyls and α -diketones by this reducing system also produced the corresponding vicinal diols.

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