SHORT PAPER

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Mild and convenient method for reduction of aliphatic and aromatic carboxylic acids and anhydrides with (pyridine)(tetrahydroborato)zinc complex as a new stable ligand-metal tetrahydroborate agent[†]

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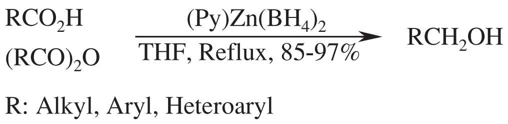
Structurally different aliphatic and aromatic carboxylic acids and anhydrides are efficiently reduced to their corresponding alcohols with a new modified zinc tetrahydroborate agent, (pyridine)(tetrahydroborato)zinc complex, [(Py)Zn(BH_4)$_2$], in refluxing THF.

Keywords: reduction, zinc tetrahydroborate, carboxylic acids, anhydrides, pyridine

Although, there are numerous literature references to the synthetic applications of various metal borohydrides,[1] only sodium borohydride has gained commercial status in spite of its poor selectivity and lesser reactivity in organic solvents. Moreover, this reagent is invariably used in excess quantities. In order to affect the reactivity of sodium borohydride, many modifications have been made upon the reagent and so various modified borohydride agents are introduced for different reduction purposes. Recently, the preparation and applications of these reagents in organic synthesis have been reviewed.[2] In fact, the reducing ability of borohydrides can be modified by: (a) hydride exchange with other substituents,[3] (b) changing of sodium cation to other metal cations,[4] quaternary ammonium[5] and phosphonium cations,[6] (c) a concurrent cation and hydride exchange,[7] (d) preparation of ligand-metal borohydrides,[8] (e) combination of borohydrides with metals, metal salts, Lewis acids[9] and finally (f) supporting on polymers.[10]

Among the reported transition metal borohydrides, zinc tetrahydroborate, $Zn(BH_4)_2$, is the only reagent which has been used frequently in the reduction reactions.[11] However, because of its requirement for storage in a cold place and instability in solid state or solution for a long time, it should always be used as its freshly prepared ethereal solutions and this situation puts some restrictions on its uses. Recently new modifications of zinc tetrahydroborate in the form of ligand–metal complexes such as $[(pyz)Zn(BH_4)_2]_n$[12], $[(dabco)Zn(BH_4)_2]$[2c,6b] and $[(Ph_3P)_x\text{-}Zn(BH_4)_2]$ (x=1, 2)[13] have been introduced and their applications in the reduction of different functional groups have been reported. These successes prompted us to prepare (pyridine)-(tetrahydroborato)zinc complex, $[(Py)Zn(BH_4)_2]$, as a new modified and stable zinc tetrahydroborate agent and investigate its reducing abilities.[14] In our preliminary investigation, we reduced structurally different aromatic and aliphatic nitro compounds efficiently to their corresponding amines.[14b] In continuation of our experiments, now we wish to report an efficient method for the reduction of aliphatic and aromatic carboxylic acids and anhydrides to their corresponding alcohols in refluxing THF (Scheme 1).

Synthetic transformation of carboxylic acids to alcohols is one of the most important reactions in organic synthesis and this goal has been achieved by several borohydride combination systems.[15-23] Zinc tetrahydroborate[24] alone or its combination system with trifluoroacetic anhydride (TFAA)[25] are the only reports of transition metal borohydrides that can reduce different aliphatic and aromatic carboxylic acids to their alcohols.



$$\begin{matrix} RCO_2H \\ (RCO)_2O \end{matrix} \xrightarrow[\text{THF, Reflux, 85-97\%}]{(Py)Zn(BH_4)_2} RCH_2OH$$

R: Alkyl, Aryl, Heteroaryl

Scheme 1

However, reduction reactions with these systems as mentioned above have some drawbacks. In the line of our interests for the preparation of new stable reducing agents on the base of zinc tetrahydroborate,[2c,12,13] we synthesised $(Py)Zn(BH_4)_2$. This reagent is easily prepared in almost quantitative yield by the complexation of 1:1 pyridine and $Zn(BH_4)_2$ in ethereal solution at room temperature (Eqns. (1) and (2)).

$$ZnCl_2 + 2NaBH_4 \xrightarrow{\text{Dry ether}} Zn(BH_4)_2 + 2NaCl \qquad (1)$$

$$Zn(BH_4)_2 + \text{Pyridine} \longrightarrow \text{Pyridine}.Zn(BH_4)_2 \qquad (2)$$

This white stable reducing agent can be stored for months in a sealed bottle without losing its activity. It is not hygroscopic or light sensitive. Structural determination of the reagent was accomplished by the atomic absorption technique, volumetric assay and elemental analysis leading to its formula as $(Py)Zn(BH_4)_2$.

Investigation of reduction reactions with this system showed that the reagent can easily reduce variety of aliphatic, aromatic and heteroaromatic carboxylic acids to their corresponding alcohols with 2–4 molar equivalents of the reagent under reflux condition. Because of the better efficiency and reactivity of the reagent in THF, this was a solvent of choice. The results of this facile reduction are summarised in Table 1 and the corresponding alcohols were obtained in high to excellent yields (90–97%). As it is evident from Table 1, the reducing agent tolerates a number of other functional groups like halogen, methoxy and nitro groups in the molecules. Reduction of cinnamic acid gives the corresponding α,β-unsaturated alcohols leading to the olefinic groups being unaffected (Entry 8). It is interesting to note that this contrasts with the behaviour of this substrate with $LiAlH_4$ where it gives 1-phenylpropanol,[26] by $Zn(BH_4)_2$/TFAA[25] where there is no reduction and by $Zn(BH_4)_2$[24] alone where the major product with accompanying double bond reduction is a mixture of 1,2-diol and 1,3-diol (ratio: 3/2) of 3-phenylpropanediol (Table 2, Entry 4). Moreover, the olefinic groups are not affected when away from the carboxylic groups. For example oleic acid on reduction with this reagent gives oleyl alcohol (Entry 16). It has been reported that dicarboxylic acids react with borane reagents[27] to give the polymeric insoluble intermediates leading to incomplete

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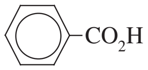
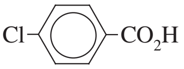
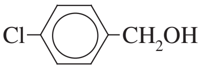
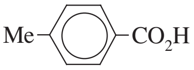
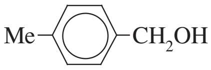
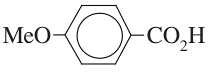
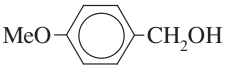
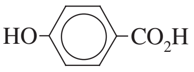
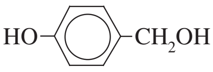
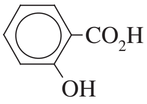
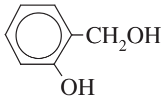
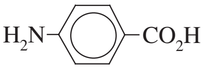
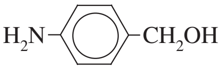
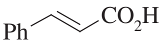
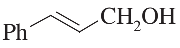
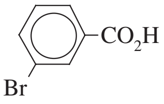
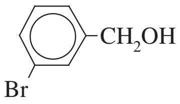
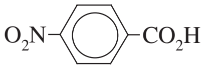
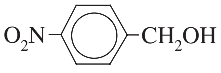
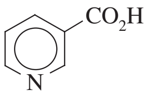
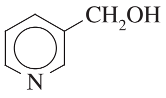
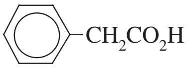
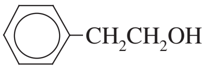
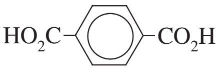
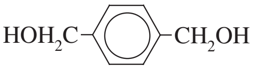
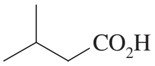
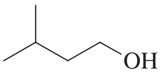
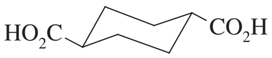
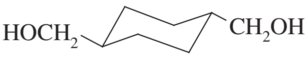
[†] This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 1: Reduction of carboxylic acids to their alcohols with $(Py)Zn(BH_4)_2$[a]

Entry	Substrate	Product	Molar ratio reag./subs.	Time/h	Yield/%[b]	M.p. or B.p./°C	
						Found	Reported[29]
1			2	1.5	96	205–206	205
2			4	3.6	93	69–71	70–72
3			3	5.1	97	60–61	59–61
4			3	6.6	96	258–259	259
5			4	3.6	92	118–120	118–122
6			3	1.5	93	82–84	83–85
7			3	2	95	63–65	60–65
8			3	4.1	90	32–34	33–35
9			3	3	96	165/16	165/16 mmHg
10			3	2.3	97	92–93	92–94
11			2	0.7	90	154/28	154/28 mmHg
12			3	1.5	97	219–220	220
13			4	7	95	117–119	117–119
14			3	0.35	90	129–130	130
15			4	0.4	96	283	283
16	$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2H$	$CH_3(CH_2)_7CH{=}CH(CH_2)_7CH_2OH$	2	0.5	94	205-206	207

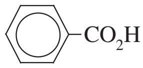
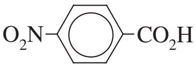
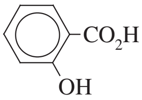
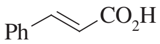
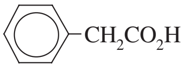
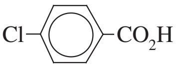
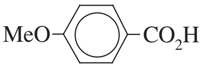
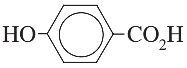
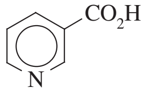
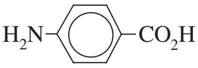
[a]All reactions were performed in THF under reflux conditions.
[b]Yields referred to isolated pure products.

reductions. However, in some cases the corresponding lactone is the major product.[28] Our reducing agent completely reduces diacids such as terephthalic acid and *trans*-1,4-cyclohexanedicarboxylic acid to the corresponding diols in high yields (Entries 13 and 15). To highlight the limitations and advantages of our method, we compared some of our results against those of reported reagents (Table 2).

In other attempt, we also compared the efficiency of isolated $(Py)Zn(BH_4)_2$ with the addition effect of pyridine to the tetrahydrofuran solution of $Zn(BH_4)_2$ in the reduction of benzoic acid. The obtained results show that at a similar time in both procedures, the isolated reagent has higher rate and efficiency in comparison to the *in situ* procedure.

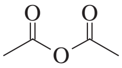
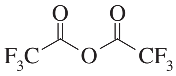
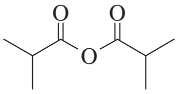
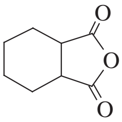
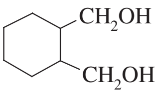
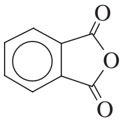
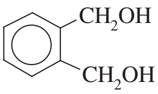
In exploring further the synthetic utility of this reducing agent we also found that symmetric aliphatic and aromatic anhydride carboxylic acids are efficiently reduced with 2–4 molar equivalents of the reagent in refluxing THF. The corresponding alcohols were obtained in high to excellent yields (85–96%). The results of this type of reduction are summarised in Table 3 and we see that the aliphatic anhydrides are reduced faster than aromatic ones with low molar ratios of the reagent.

Table 2: Comparison of reduction of carboxylic acids to their alcohols with (Py)Zn(BH$_4$)$_2$ and other reported reagents

Entry	Substrate	Molar ratio[a], Time/h and Yield/%					
		I	II[24]	III[23b]	IV[16a]	V[17]	VI[15d]
1		2(1.5)(96)	3.3(6)(90)	MR[b](1)(74)	MR[c](1.3)(93)	MR[d](5)(92)	4(1)(89)
2		3(2.3)(97)	3.3(4)(90)	MR[b](1)(75)	–	MR[d](2.5)(94)	–
3		3(1.5)(93)	4.4(4)(0)	–	MR[c](1.3)(92)	–	5(3)(92)
4		3(4.1)(90)	4.4(5)(90)[e]	MR[b](1)(80)	MR[c](1.3)(97)	–	–
5		4(7)(95)	6.6(5)(70)	–	–	–	–
6		3(1.5)(97)	3.3(3)(95)	–	MR[c](1.3)(98)	MR[d](4)(88)	–
7		4(3.6)(93)	–	MR[b](1.3)(88)	MR[c](1.3)(98)	–	
8		3(6.6)(96)	–	MR[b](1)(93)	–	MR[d](4.5)(97)	–
9		4(3.6)(92)	–	MR[b](1)(83)	–	–	–
10		2(0.7)(90)	–	MR[b](2)(85)	–	–	–
11		3(2)(95)	–	–	–	–	8(4.5)(80)

[I](Py)Zn(BH$_4$)$_2$; [II]Zn(BH$_4$)$_2$; [III]BER/Ni(OAc)$_2$; [IV]NaBH$_4$/I$_2$; [V]PhCH$_2$NEt$_3$BH$_4$/Me$_3$SiCl; [VI]BH$_3$-THF; [a]Molar Ratio as Reagent/Substrate; [b]BER/Ni(OAc)$_2$/Substrate: 3/0.08/1; [c]NaBH$_4$/I$_2$/Substrate: 1.2/0.5/1;[d]BH$_4$-/Me$_3$SiCl/Substrate: 2/2/1; [e]Product as mixture of 1,2-diol and 1,3-diol (ratio: 3/2) of 3-phenylpropanediol

Table 3: Reduction of anhydride carboxylic acids to their alcohols with (Py)Zn(BH$_4$)$_2$[a]

Entry	Substrate	Product	Molar ratio reag./subs.	Time/h	Yield/%[b]	M.p. or B.p./°C	
						Found	Reported[29]
1		CH_3CH_2OH	2	1.5	90	78–79	78–79
2		CF_3CH_2OH	2	1	85	77–78	77–80
3		$CH_3(CH_3)CHCH_2OH$	2	2.5	92	108–109	108
4			3	0.8	93	44–45	43–45
5			4	6	96	64	63–65

[a]All reactions were performed in THF under reflux conditions.
[b]Yields referred to isolated pure products.

In conclusion, the usefulness of this methodology lies in the fact that pyridine stabilises $Zn(BH_4)_2$ in the form of $(Py)Zn(BH_4)_2$ for easy handling and storage. This new stable ligand-metal borohydride can efficiently reduce a variety of aliphatic, aromatic and heteroaryl carboxylic acids under mild condition. Reduction of diacids and conjugated or non-conjugated compounds to their alcohols was easily achieved without affecting the olefinic bond and formation of polymeric compounds. This reagent also efficiently reduces anhydride carboxylic acids with fast reduction of aliphatic compounds relative to the aromatic ones. Stability of the reagent relative to $Zn(BH_4)_2$, a simple procedure, mild reaction conditions, easy work-up of the reaction mixture and the high yields of the products are noteworthy advantages of this system and make it a useful addition to the present methodologies in this area.

Experimental

All products were characterised by a comparison of their physical data with those of authentic samples (IR, ^1H NMR and m.p. or b.p.). All yields referred to isolated products. TLC accomplished the purity determination of the substrates, products and reactions monitoring over silica gel PolyGram SILG/UV 254 plates.

Preparation of (pyridine)(tetrahydroborato)zinc complex; $(Py)Zn(BH_4)_2$: 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 established procedure in the literature.[30] Then, a solution of pyridine (3.164 g, 0.04 mol) in ether (50 ml) was added drop wisely to the ethereal solution of $Zn(BH_4)_2$ and stirred for 30 min. Evaporation of the solvent under vacuum at room temperature gave $(Py)Zn(BH_4)_2$ in nearly quantitative yield (6.83 g, 98%) which was decomposed to the dark material at 106-108°C.[14] Found: C, 34.33; H, 7.61; N, 7.99; Zn, 37.44 %. Calculated for $C_5B_2H_{13}NZn$: C, 34.48; H, 7.52; N, 8.04; Zn, 37.54 %.

Reduction of benzoic acid to benzyl alcohol with $(Py)Zn(BH_4)_2$: a typical Procedure. In a round-bottom flask equipped with magnetic stirrer and condenser, a solution of benzoic acid (0.122 g, l mmol) in THF (5 ml) was prepared. Then the reducing agent (0.35 g, 2 mmol) was added and the reaction mixture was stirred under reflux condition for 1.5 h. TLC monitors the progress of the reaction. After completion of the reaction, the mixture was quenched with dilute HCl (5 ml, 3 N) and the aqueous layer was extracted with CH_2Cl_2 (3×10 ml). The combined organic extracts was washed with NaOH (1N, 10 ml), water, brine solution and dried over anhydrous Na_2SO_4. Evaporation of the solvent and column chromatography of crude material over silica gel with eluent of CCl_4/ether: 5/2 affords pure liquid benzyl alcohol (0.088 g, 96% yield).

Reduction of phthalic anhydride to 1,2-benzenedimethanol with $(Py)Zn(BH_4)_2$: a typical procedure: In a round-bottom flask equipped with magnetic stirrer and condenser, a solution of phthalic anhydride (0.148 g, 1 mmol) in THF (5 ml) was prepared. Then the reducing agent (0.71 g, 4 mmol) was added and the reaction mixture was stirred under reflux condition for 6 h. The progress of reaction was monitored by TLC. After completion of the reaction, the mixture was quenched with dilute HCl (5 ml, 3 N) and the aqueous layer was extracted with CH_2Cl_2 (3×10 ml). The combined organic extracts was washed with NaOH (1N, 10 ml), water, brine solution and dried over anhydrous Na_2SO_4. Evaporation of the solvent and column chromatography of crude material over silica gel with eluent of CCl_4/Ether: 5/2 affords pure crystals of 1,2-benzenedimethanol (0.1 g, 96% yield).

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