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# ZIRCONIUM BOROHYDRIDE - A VERSATILE REDUCING AGENT FOR THE REDUCTION OF ELECTROPHILIC AND NUCLEOPHILIC SUBSTRATES

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Abstract: Zirconium borohydride, a potential reducing agent, reduces acids, esters, imines to the corresponding alcohols and secondary amines in good yield at room temperature within two hours. This facile reducing property was taken advantage off in the synthesis of pheromones and some novel chiral precursors for asymmetric synthesis.

In the course of our study on the reduction of metal borohydrides like lithium, calcium, zinc and tetrabutylammonium borohydrides, significant differences in the reactivity was observed depending on the counter ion of the borohydride. Zinc borohydride exhibited excellent reactivity towards a variety of functional groups like acids, esters, amides etc., revealing its predominant electrophilic nature<sup>1</sup>. These substrates were reduced in excellent yield to the corresponding alcohols and N-ethyl

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amines in refluxing THF. In view of this, we extended our studies to another transition metal borohydride having a variable valency, zirconium borohydride. Accordingly, zirconium borohydride was prepared by the metathesis reaction of sodium borohydride and zirconium tetrachloride in THF. The hydride content of the zirconium borohydride solution was estimated by withdrawing aliquot of supernatant solution and quenching with 3N  $H_2SO_4$  and measuring the volume of  $H_2$  librated. The solution was used as such for reductions.

#### Electrophilic reductions:

*Reduction of acids:* Zirconium borohydride reduces acids at much faster rate than zinc borohydride (which requires 5h in refluxing THF<sup>2</sup>) and tetrabutylammonium borohydride also requiring 5h in refluxing CHCl<sub>3</sub>.<sup>3</sup> Aliphatic, aromatic acids were reduced within 2h, while the reduction of methyl 10-undecenoate, a unsaturated acid was over within 15min. and amino acids were reduced within 3h. Quantitative conversion to alcohols was observed in all these cases. Unsaturated acids were reduced to the corresponding diols in over 90% yield.

$$CH_{2}=CH(CH_{2})_{8}COOH \xrightarrow{(i)Zr(BH_{4})_{4}/THF} HOCH_{2}(CH_{2})_{8}CH_{2}OH$$

$$(CH_{3})_{2}CHCHCOOH \xrightarrow{(i)H_{2}O_{2}/OH} \underbrace{Zr(BH_{4})_{4}/THF}_{NH_{2}} \xrightarrow{(CH_{3})_{2}CHCHCH_{2}OH} (CH_{3})_{2}CHCHCH_{2}OH$$

Amino acids were reduced to the corresponding amino alcohols at room temperature using stoichiometric quantities of hydride unlike borane (which requires two equivalents per mole of the substrate<sup>1</sup>) (Table 1). This observation was used in the synthesis of various pheromones. Thus, 1,9nonane diol was obtained by the reduction of azelaic acid, which is a key step in the synthesis of Z-9-hexadecenol, an important pheromone constituent of lepidopteran pests<sup>4</sup>.

*Reduction of amides:* Since zirconium borohydride behaves like an electrophilic reagent, its utility in the reduction of amides were explored. The reaction proceeded with stoichiometric quantities of hydride at room temperature to give the corresponding secondary amines in good yield. Here again, the problem of an additional equivalent of borane required for the N-BH<sub>3</sub> coordination, has been avoided. As observed for the reduction of acids the reaction proceed smoothly at room temperature, an advantage over zinc borohydride and tetrabutylammonium borohydride which required reflux conditions. Thus a variety of amides were reduced to the corresponding N-ethylanilines. (Table 1)

$$-NHCOCH_3 - \frac{Zr(BH_4)_4/THF}{25^0C, 2h} - NHCH_2CH_3$$

 $X = Cl, Br, NO_2, OMe$ 

	ACIDS	
Substrate	Product	°Yield (%)
Palmitic acid <sup>a</sup>	1-Hexadecanol	95
Myristic acid <sup>a</sup>	Myristyl alcohol	95
Azelaic acid <sup>b</sup>	1,9-Nonanediol	90
Brassylic acid <sup>b</sup>	1,13-Tridecanediol	95
Benzoic acid <sup>a</sup>	Benzyl alcohol	90
4-Nitrobenzoic acid <sup>a</sup>	4-Nitrobenzyl alcohol	97
Terephthalic acid <sup>b</sup>	1,4-Bis-[hydroxymethyl]	91
-	benzene	
Acetyl salicylic acid <sup>a</sup>	Salicyl alcohol	90
Undecenoic acid <sup>c</sup>	1,11-Undecanediol	90
Valine <sup>a</sup>	3-Methyl-2-amino-1-propanol	91
Phenyl alanine <sup>a</sup>	3-Phenyl-2-amino-1-propanol	90
	AMIDES <sup>*</sup>	
Acetanilide	N-Ethylaniline	90
3-Chloroacetanilide	N-Ethyl-3-chloroaniline	90
4-Bromoacetanilide	N-Ethyl-4-bromoaniline	90
4-Methoxyacetanilide	N-Ethyl-4-methoxyaniline	92
3,3-Dichloroacetanilide	N-Ethyl-3,4-dichloroaniline	90
4-Bromo-3-chloroacetanilide	N-Ethyl-4-bromo-3-	90
	chloroaniline	
benzanilide	N-Benzylaniline	92
2-Nitroacetanilide	N-Ethyl-2-nitroaniline	90
<sup>a</sup> [Substrate] $\cdot$ [H-] = 1:3: <sup>b</sup> [s	ubstrate] : [H-] = 1:6 : °[substr	ate] : $[H_{-}] = 1:4$

## Table 1 Reduction of acids and amides using Zirconium borohydride

# Nucleophilic reductions:

*Reduction of esters:* Unlike tetrabutylammonium borohydride, which does not reduce esters<sup>5</sup>, zirconium borohydride reduced esters to the corresponding alcohols in good yield as evidenced by the reduction of methyl 10-undecenoate to undecandiol. A number of esters were reduced to show the efficiency of this reagent in reducing the ester group.(Table 2)

Substrate	Product	Yield %
E	STERS	
Methyl 10-undecenoate <sup>c</sup>	1,11-Undecanediol	93
Methyl myristate <sup>b</sup>	Myrsityl alcohol	95
Methyl laurate <sup>b</sup>	1-Dodecyl alcohol	90
Ethyl benzoate <sup>b</sup>	Benzyl alcohol	91
dimethyl brassylate <sup>d</sup>	1,13-Tridecanediol	93
dimethyl terephthalate <sup>d</sup>	1,4-Bis[hydroxy methyl] benzene	92
Ethyl 2-chlorobenzoate <sup>b</sup>	2-Chloro benzyl alcohol	95
Methyl 4-nitrobenzoate <sup>b</sup>	4-Nitro benzyl alcohol	95
Methyl 4-hydroxybenzoate <sup>c</sup>	4-Hydroxy benzyl alcohol	96
<b>I</b>	MINES	
N-(3-Chlorophenyl)imino-2- hydroxy benzaldehyde <sup>b</sup>	N-(3-Chlorophenyl)2- hydroxy benzylamine	95
N-(4-Chlorophenyl)imino benzaldehvde <sup>a</sup>	N-(4-Chlorophenyl) benzyl amine	94
N-(1-Carbomethoxy-2-methyl) propyl imino-2-hydroxy benzaldehyde <sup>d</sup>	2-(N-2- Hydroxybenzyl) amino-3-methyl-1- butanol	92
N -(1-Carbomethoxy-2-phenyl) ethylimino -2-hydroxy benzaldehyde <sup>d</sup>	2-(N-2- Hydroxybenzyl) amino-4-methyl-1- pentanol	95
N-Benzyliminoacetophenone <sup>®</sup>	N-(Benzyl)-1-phenyl ethylamine	94
N,N'-Biscyclohexyl ethylenediimine <sup>d</sup>	N,N'-Bis-[cyclohexyl ethylene] diamine	90
N.N'-Bis(2-hydroxybenzyl) ethylene diimine <sup>d</sup>	N,N'-Bis(2-hydroxy benzyl) ethylene diamine	94
<sup>a</sup> [Substrate]: $[H^{-}] = 1: 1$ <sup>b</sup> [Substrate]: $[H^{-}] = 1: 4$	ubstrate]: $[H^{T}] = 1:2$ <sup>c</sup> [Substrate]	ate] : $[H^-] = 1: 3$

|--|

<sup>[</sup>Substrate] : [H] = 1:4



Reduction of imines: Zirconium borohydride also reduces aldimines, ketimines and diimines to the corresponding secondary amines(Table 2). This reaction was utilised in the one pot reduction of imine esters to  $\beta$ amino alcohols, as characterised by 1D and 2D NMR experiments. This reduction of imine esters were complete in less than 2h giving more than 90% yield.



In conclusion, we have found that zirconium borohydride can be used as an effective substitute for borane due to its economic use of available hydride and safety in handling. The advantage of this reagent over its other analogs viz., zinc, calcium or tetrabutylammonium borohydrides is that the reactions proceeds rapidly at room temperature with good yields of the products.

#### **Typical experimental procedures:**

All the reactions were carried out under nitrogen atmosphere.

Preparation of zirconium borohydride: A 500 mL round-bottomed flask equipped with a magnetic pellet and fitted with reflux condenser is flame dried under a stream of nitrogen. To this cooled assembly,13.9 g (60 mmol) of zirconium tetrachloride was added followed by the addition of 9.12 g (240 mmol) of sodium borohydride. 250 mL of dry THF was then added through a double ended needle and the contents were stirred at room temperature for 2 days. The clear supernatant solution was estimated for its hydride content and used as such for reactions.

The hydride content of the zirconium borohydride solution was used for all the reactions was 3M in H<sup>-</sup>.

a: General procedure for the reduction of acids: Reduction of palmitic acid:To 0.5 g (5 mmol) of palmitic acid in 5 mL of THF, 5 mL of zirconium borohydride solution was added and the reaction mixture was stirred at room temperature for 1h. The excess hydride was quenched by adding 1 mL of 3N H<sub>2</sub>SO<sub>4</sub>. The reaction mixture was extracted twice with THF and dried over anhydrous K<sub>2</sub>CO<sub>3</sub>. The solvent was removed under reduced pressure to yield 1.1 g (Yield 95%) of 1-hexadecanaol melting at 55 °C (56 °C)<sup>lit</sup>.

Reduction of 10-undecenoic acid. (involves oxidative work up) : To 1 mL (5 mmol) of 10-undecenoic acid in 5 mL of THF, 6.6 mL of zirconium borohydride solution was added and the reaction mixture was stirred at

room temperature for 1h. The excess hydride was quenched by adding 1 mL of  $3N H_2SO_4$  and then made alkaline with NaOH solution followed by oxidation with  $30\% H_2O_2$ . The organic layer was separated, washed with NaOH and dried over anhydrous K<sub>2</sub>CO<sub>3</sub>. The solvent was removed under reduced pressure to yield 0.85 g (Yield 90%) of 1,11-undecanediol melting at 60 °C (61 °C)<sup>lit</sup>.

b.*Reduction of amides: Reduction of acetanilide*: To 0.65 g (5 mmol) of acetanilide in 5 mL of zirconium borohydride solution was added and the contents were stirred at room temperature for 2h. The excess hydride was quenched by adding 1 mL of methanol and the reaction mixture was extracted twice with THF and dried over anhydrous  $K_2CO_3$ . The solvent was removed under reduced pressure to yield 0.54 g of N-ethylaniline. (Yield 90%)

c.Reduction of esters: Reduction of Methyl myristate: 3.6 mL of zirconium borohydride solution was added to 1.21 g (5 mmol) of methyl myristate in 5 mL of THF and the contents were stirred for 2h at room temperature. The excess hydride was quenched by adding 2mL of methanol and worked up as above. Removal of solvent under reduced pressure yielded 1 g (Yield 95%) of myristyl alcohol melting at 38 °C (40 °C)<sup>lit</sup>.

d. Reduction of imines: Reduction of N-(1-carbomethoxy-2methyl)propylimino-2-hydroxy benzaldehyde: 1.2 g of N-(1carbomethoxy-2-methyl)propylimino-2-hydroxybenzaldehyde (5 mmol) in 10 mL of dry THF was stirred with 6.6 mL of zirconium borohydride solution for 2h at room temperature. The reaction was quenched with methanol. THF was removed under reduced pressure. pH was adjusted to approximately 8 by adding aq. NaOH solution and the free amine formed was extracted in chloroform. The chloroform extract was dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure to yield the product.(Yield 92%).

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