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S. Narasimhan^a, S. Madhavan^a & K. Ganeshwar Prasad^a

^a Centre for Agrochemical Research, SPIC Science Foundation, Guindy, Madras, 600 032, INDIA

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A Simple Alkene -Catalyzed Reduction of Aromatic Esters to Alcohols by Zinc Borohydride

S. Narasimhan*, S. Madhavan and K. Ganeshwar Prasad. Centre for Agrochemical Research, SPIC Science Foundation, Guindy, Madras 600 032. INDIA.

Abstract: Reactivity of $Zn(BH_4)_2$ was modified by adding cyclohexene to achieve the reduction of aromatic esters to alcohols which reaction was not possible previously because of the mild nature of the reagent. Functional groups like Cl and nitro were tolerated.

Zinc borohydride, a mild reducing $agent^1$ is finding increasing applications in synthetic transformations such as reduction of carbonyl compounds, selective reduction of aldehydes over ketones², α , β -unsaturated aldehydes over α , β -enones³ and also reduction of an aliphatic ester in the presence of an aromatic ester⁴. However, enhancing the reactivity of Zn(BH₄)₂ could make it a versatile reagent in synthetic applications. A simple method to achieve this would be to add reagents such as R₃B, R₂BOR etc., which are shown to be very powerful catalysts in the reduction of esters (Scheme 1) by lithium borohydride⁵.

 $\begin{array}{rcl} \text{RCOOMe} &+ \text{LiBH}_4 & \xrightarrow{\text{R}_2\text{BOR'}} & \text{RCH}_2\text{OH} \\ & & & & \\$

Scheme 1

^{*} To whom all correspondence should be addressed

Interestingly, the reduction of esters by $LiBH_4$ also induced hydroboration of unsaturated compounds⁶. This prompted us to explore the possibility of generating the catalyzing species *in situ* by adding any olefin in the reaction with $Zn(BH_4)_2$. A preliminary study on the rate of reduction of representative esters by $Zn(BH_4)_2$ in THF would indicate the occurrence of tandem reduction-hydroboration reaction.

Accordingly, rate of reduction of esters by $Zn(BH_4)_2$ in refluxing THF was studied by withdrawing aliquots at various intervals and quenching the aliquots using $3N H_2SO_4$. The active hydride concentration and hence the hydride consumed for the reduction was found out by measuring the quantity of hydrogen evolved. Following this procedure we observed that the reduction of methyl myristate was complete in 5h while methyl benzoate was reduced to only 9 % in 4h. On the other hand, methyl 10-undecenoate formed a gel within 30 min. and the reaction mixture when quenched as a whole after 1h resulted in 3H⁻ uptake/ester indicating concomitant reduction-hydroboration of the ester (Table 1).

Therefore, addition of catalytic quantity of an olefin to the reaction mixture containing $Zn(BH_4)_2$ and ester should form the required boronate which would enhance the reactivity of the reagent. Thus, addition of 10 mole % of cyclohexene

Ester	% Reaction						
	0.25h	0.5h	1h	2h	4h	5h	
Methyl myristate	1.5	4.5	14.5	61.0	93.5	97.5	
Methyl benzoate				4	9		
Methyl 10-undecenoate		gel	98*				

Table 1. Rate of reduction of esters by Zn(BH₄)₂ in refluxing THF

*whole of reaction mixture was quenched; based on 3H- uptake/ ester

REDUCTION OF AROMATIC ESTERS

Methyl ester	Catalyst (mole %)	% Reaction					
		0.25h	0.5h	1h	2h	4h	5h
Myristate	0	1.5	4.5	14.5	61.0	93.5	97.5
	10	36.0	64.0	84.0	104		
Benzoate	0				4	9	
	10	8.5	16	33.5	60	87	101
2-Cl-benzoate	0	15.5	23.5	33.5	43	53	60.5
	10	26	28	49.5	86.5	105	

Table 2. Reduction of esters by $Zn(BH_4)_2$ in the presence of cyclohexene as catalyst

to the reaction mixture containing $Zn(BH_4)_2$ and an aliphatic ester, namely, methyl myristate, shortened the reaction time to 2h from 5h (for the uncatalyzed reaction). Even methyl benzoate, which was not reduced by $Zn(BH_4)_2$ previously (9% in 4h) was reduced quantitatively in 4h (Table 2).

Typically, addition of any olefin, such as, cyclohexene, to the reaction mixture containing borohydride and an ester results in the hydroboration of the olefin which then dissociates to form dicyclohexylborinate. This forms dicyclohexyl borohydride species through an exchange reaction with BH₄⁻ ion. The former, due to its increased nucleophilic character (similar to Li 9-BBNH),⁷ rapidly reduces even the less reactive aromatic esters completely.

A number of functional groups are tolerated providing selectivity towards ester reduction. However, unsaturated compounds undergo hydroboration which can be utilised for conversions where simultaneous reduction-hydroboration is required (Table 3). This method would increase the versatility and scope of application of $Zn(BH_4)_2$ in synthetic applications.

Tuolo 5, requiring of esters of			in the second start star				
1	R	Time	7	R	Yield		
		(h)			(%)		
a	C ₆ H ₅	5	a C ₆ H ₅		72		
b	$2-Cl-C_6H_4$	4	b	$2-Cl-C_6H_4$	83		
c	$3-O_2N-C_6H_4$	3	c	$3-O_2N-C_6H_4$	80		
d	$4-O_2N-C_6H_4$	3	d	$4-O_2N-C_6H_4$	75		
e	4-HO-C ₆ H ₄	4	e	4-HO-C ₆ H ₄	72		
f	2-HO-C ₆ H ₄	4	f	2-HO-C ₆ H ₄	70		
g	4-MeOOC-C ₆ H ₄	2	g	4-HOCH ₂ -C ₆ H ₄	70		
h	C ₆ H ₅ CH ₂	2	h	C ₆ H ₅ CH ₂	75		
i	CH ₃ (CH ₂) ₁₂	2	i	CH ₃ (CH ₂) ₁₂	76		
j	CH ₂ =CH-(CH ₂) ₈ *	2	j	HO-(CH ₂) ₁₀	80		
k	MeOOC-(CH ₂) ₁₁	4	k	HO-(CH ₂) ₁₂	76		

Table 3. Reduction of esters by $Zn(BH_4)_2$ in refluxing THF⁹.

* Cyclohexene was not used.

Experimental Procedure : Preparation of Zinc borohydride : Zinc borohydride was prepared by the metathesis reaction of sodium borohydride with zinc chloride. Typically to 6.65g of sodium borohydride (175 mmol) in a side armed flask assembled hot and cooled under nitrogen was added 11.9g (87.5 mmol) of zinc chloride followed by 250 mL of dry THF (distilled under nitrogen and stored over sodium) and the contents were stirred at room temperature for 24 hours. The stock solution was used as such for further reactions.

Typical procedure for rate study : To 1.7 mL (2.75 mmol) of zinc borohydride (0.71 M solution of $BH4^-$ in THF) and 50 μ L (0.5 mmol) of cyclohexene was added followed by 0.68g (5 mmol) of methyl benzoate and the total volume of the solution was made up to 10 mL with THF. The contents were refluxed and the rate of the reduction was followed by quenching 0.25 mL aliquots of the reaction

mixture at various time intervals with $3N H_2SO_4$ and measuring the volume of hydrogen evolved.

Typical procedure for reduction: Reduction of methyl 2-chlorobenzoate is representative. 0.87g (5 mmol) of the ester was added to 3.8 mL of zinc borohydride(2.75 mmol of BH₄⁻) and cyclohexene (50 μ L, 0.5 mmol) and was refluxed under nitrogen for 4 hours. The excess borohydride was quenched by adding 2 mL of aqueous methanol(50% v/v). The solution was saturated with potassium carbonate and the THF layer was separated. The residue was extracted with THF and the combined extracts were dried over anhydrous K₂CO₃. The solvent was removed under reduced pressure to yield 0.58g (83 %) of 2chlorobenzyl alcohol melting at 72°C (Lit. 74°C).

1,11-Undecane diol (1j): To 0.99g (5 mmol) of methyl 10-undecenoate was added 7 mL (5 mmol of BH₄⁻, 0.71M in BH₄⁻ in THF) and the contents were refluxed for 2h. The excess borohydride was quenched with MeOH and the solution was made alkaline with NaOH (3M) and was oxidized with 30 % H₂O₂ (2 mL). The product was isolated as above. 0.75g (80 %) of 1,11-undecane diol was obtained melting at 60°C (Lit. 61°C).

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- 9. The reductions were carried out using stoichiometric quantities of hydride using 10 mole% of cyclohexene as catalyst; the products were characterized by spectral data, melting point and by comparison with standard samples.

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