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Use of Zinc Borohydride for Efficient Reduction of Carboxylic Ester to Alcohol. Selective Reduction of Aliphatic Ester in Presence of Aromatic Ester Under Sonication

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Key Words: zinc borohydride; selective carboxylic ester reduction; sonication

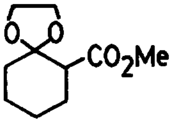
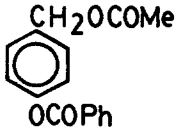
Abstract: An efficient methodology using zinc borohydride under sonication for the reduction of carboxylic esters to alcohols in presence of N,N-dimethylaniline and selective reduction of an aliphatic ester over an aromatic one without N,N-dimethylaniline is described.

Selective reduction of one out of two different carboxylic ester groups to alcohol through a simple and mild operation is a challenging problem in the field of organic synthesis. Inspite of a number of reagents available for efficient ester reduction, none is suitable for this selective transformation.[1] The most commonly used reagent for the reduction of a carboxylic ester is lithium aluminium hydride which, being a powerful reducing agent, obviously can not discriminate between two ester groups. Borohydrides [$NaBH_4$, $LiBH_4$, $Ca(BH_4)_2$] under normal conditions do not attack esters but under certain special measures are reported to effect ester reduction.[2] However, this appears to occur without any such discrimination. As a part of our continuing efforts to explore the novel uses of zinc borohydride[3] we have discovered that this reagent[4,5] under ultrasonic activation offers an excellent selectivity toward reduction of aliphatic carboxylic esters, over aromatic ones. We have also observed that this reduction under sonication is much accelerated with the presence of N,N-dimethylaniline in the system. The results of this investigation are presented herein.

In a typical procedure, the carboxylic ester (1 mmol) was treated with a solution of zinc borohydride (1 mmol) in 1,2-dimethoxyethane under sonication for a certain period of time (Table-1). The reaction mixture was then decomposed with H_2O and extracted with CH_2Cl_2. Evaporation of solvent furnished the corresponding alcohol in nearly quantitative yield. The results are reported in Table-1.

As shown in Table-1, aliphatic carboxylic esters were reduced to the corresponding alcohols (entries 1-5, procedure A), whereas under identical reduction conditions the aromatic esters remained inert (entries 6-10, procedure A).[6] Under similar treatment benzyl acetate was cleaved to benzyl alcohol, whereas benzyl benzoate remained partically intact (entries 11,12, procedure A). Thus, under this procedure, acetates were selectively deblocked in presence of benzoates[7] (entry 13, procedure A). Interestingly, the reduction was highly accelerated by the presence of a catalytic amount[8] of N,N-dimethylaniline.[9] Aliphatic esters were reduced much faster and the aromatic esters which remained inert under procedure A were now reduced efficiently under the conditions of procedure B.

Table-1 : Reduction of carboxylic esters with zinc borohydride to the corresponding alcohols under sonication

		procedure A[a]		procedure B[b]	
entry	carboxylic ester	time,h	% reduction[c]	time,h	% reduction[c]
1	methyl cyclohexanecarboxylate	24	100	14	100
2	methyl phenylacetate	18	100	12	100
3	ethyl 3-bromopropionate	18	100	12	100
4	$MeO_2C-(CH_2)_8-CO_2Me$	24	100	14	100
5		24	100	-	-
6	methyl benzoate	24	0	24	100
7	methyl 4-methoxybenzoate	24	0	24	100
8	methyl 4-nitrobenzoate	24	0	24	100
9	methyl 4-chlorobenzoate	24	0	24	100
10	ethyl 4-methylbenzoate	24	0	24	100
11	$PhCH_2OCOMe$	24	100	-	-
12	$PhCH_2OCOPh$	24	5	-	-
13		24	100(acetate) 0 (benzoate)	-	-

[a] Without N,N-dimethylaniline; [b] with N,N-dimethylaniline (2 drops); [c] % reduction as calculated by ^1H NMR analysis.

As carboxylic esters remain unaffected by zinc borohydride without sonication as observed by us and other workers[3a,5d,5e] certainly ultrasonic waves improve the reductive properties of zinc borohydride.[10,11] Acceleration of reduction with

N,N-dimethylaniline, though interesting, is not unprecedented.[5e] Whatever be the exact nature of activation, the synthetic utility of this methodology cannot be ignored and to the best of our knowledge this is the first systematic study of selective reduction of an aliphatic carboxylic ester group in presence of an aromatic one[12] as well as the use of zinc borohydride for efficient reduction of ester.

Zinc borohydride is neutral and can thus be employed to effect reductions in the presence of functional groups which are sensitive to the more basic conditions of reduction with $LiAlH_4$ and $NaBH_4$. Moreover, compatibility of this procedure with a variety of normally reducible functional groups such as, bromo, chloro, nitro, ketal, makes it more useful for selective ester reduction in polyfunctional molecules. Unfortunately, conjugated olefinic esters cannot be reduced under this procedure without involvement of the double bond.

In summary, the present methodology using zinc borohydride under sonication provides an efficient reduction of an ester to an alcohol through a mild and simple operation. Particularly noteworthy are the selective reductions of a saturated aliphatic carboxylic ester over an aromatic one and selective deblocking of an acetate in the presence of a benzoate with a neutral hydride reagent. We believe, this procedure will certainly find suitable and significant application in the field of organic synthesis. Further work to optimize the condition for conjugated ester reduction as well as to uncover the role of N,N-dimethylaniline for acceleration are in progress.

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4. Though convenientlv employed for the reduction of ketonic carbonyl compounds,[5] zinc borohydride is reported to be inert towards carboxylic ester.[3a,5d,5e]

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6. When a 1:1 mixture of methyl cyclohexanecarboxylate and methyl benzoate were treated with zinc borohydride in DME under sonication for 24 h, methyl benzoate was recovered unchanged and cyclohexylmethanol was obtained quantitatively.

7. In a competition experiment with a 1:1 mixture of benzyl acetate and benzyl benzoate with zinc borohydride in DME under sonication for 24 h, benzyl benzoate was recovered unchanged while benzyl acetate was cleaved to benzyl alcohol quantitatively.

8. For comparison, the reduction was carried out with a catalytic amount (2 drops), 1 equiv. and 2 equiv. of N,N-dimethylaniline; the rate of acceleration (conversion) was found more or less same.

9. N,N-dimethylaniline was found to be the best choice among triethylamine, pyridine and N,N,N',N'-tetramethylethylenediamine.

10. For use of ultrasonic waves in reduction and other areas of organic synthesis, see : (a) Petrier, C.; Luche, J.-L. Tetrahedron Lett. **1987**, 28, 2347. (b) Brown, H.C.; Racherla, U.S. Tetrahedron lett. **1985**, 26, 2187. (c) Einhorn, C.; Einhorn, J.; Luche, J.-L. Synthesis **1989**, 787 and references cited therein. (d) Abdulla, R.F. Aldrichim. Acta. **1988**, 21, 31 (e) Lindley, J.; Mason, T.J. Chem. Soc. Rev. **1987**, 16, 275.

11. For comparison, when $NaBH_4$ was used in place of $Zn(BH_4)_2$, no reduction occurred.

12. Very recently sodium borohydride-copper(II) sulphate system has been reported to reduce selectively an aliphatic ester over an aromatic one (one example) (Yoo, S.; Lee, S. Synlett. **1990**, 419).

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