

## Selective Reduction of Carboxylic Acids with Zinc Borohydride in the Presence of Trifluoroacetic Anhydride

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A simple and convenient procedure for the reduction of carboxylic acids to the corresponding alcohols has been developed using a solution of zinc borohydride in 1,2-dimethoxyethane in the presence of trifluoroacetic anhydride.

Metal borohydrides are very important and widely used reducing agents in organic synthesis. Their reactivities are remarkably influenced by the metal ion,<sup>1</sup> the solvent<sup>1,2</sup> and the presence of catalysts or additives.<sup>3</sup> By variation of these factors borohydrides have been utilized for various selective and useful reductions.<sup>1,4</sup> Carboxylic acids, which remain inert with borohydrides under ambient conditions,<sup>4,5</sup> are reduced to the corresponding alcohols with  $\text{LiBH}_4$  ( $\text{NaBH}_4$ )- $\text{Me}_3\text{SiCl}$ ,<sup>3</sup>  $\text{NaBH}_4$ - $\text{I}_2$ ,<sup>6a</sup>  $\text{NaBH}_4$ -catechol,<sup>6b</sup>  $\text{NaBH}_4$ - $\text{CF}_3\text{CO}_2\text{H}$ <sup>6b</sup> and benzyltriethylammonium borohydride- $\text{Me}_3\text{SiCl}$ .<sup>6c</sup> Carboxylic acids are also reduced to alcohols by  $\text{LiAlH}_4$  and  $\text{B}_2\text{H}_6$ .<sup>1,5a</sup> Although, these reagents are satisfactory for the reduction of simple acyclic carboxylic acids, many of these methods have limited use for secondary and aromatic carboxylic acids containing sensitive functionalities. Our recent experience of the reduction of various functionalities with zinc borohydride<sup>7</sup> reveals that this borohydride is different from other metal borohydrides and its reactivity lies between that of diborane and sodium borohydride. Thus, we considered it interesting and remunerative to study the reaction of carboxylic acids with zinc borohydride.

We have observed that carboxylic acids, in general, are resistant to reduction with zinc borohydride in DME (1,2-dimethoxyethane), although some straight chain carboxylic acids† are found to undergo very slow reductions. Interestingly, the presence of trifluoroacetic anhydride (TFA) promotes the

reactivity of zinc borohydride and the reduction is accelerated significantly. In a typical procedure, a mixture of carboxylic acid and TFA is stirred with zinc borohydride in DME at room temperature. The product was isolated in a pure state by simple extraction with diethyl ether after decomposition with water. The results are reported in Table 1.

As shown in Table 1, several structurally varied carboxylic acids were reduced to the corresponding alcohols in good yields with the  $\text{Zn}(\text{BH}_4)_2$ -TFA reagent system. Straight chain aliphatic carboxylic acids underwent faster reduction than aromatic carboxylic acids. Thus homophthalic acid (entry 12) produces the corresponding  $\delta$ -lactone, formed by the selective reduction of the acetic acid moiety followed by its lactonisation with the aromatic carboxylic group. The carboxylic ester (entry 14) remained unaffected by this procedure.

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  $\text{LiAlH}_4$  and  $\text{NaBH}_4$ . Moreover, the compatibility of this procedure with a variety of normally reducible functional groups such as, chloro, nitro and carboxylic ester groups and isolated double bonds makes it more useful for selective carboxylic acid reduction in polyfunctional molecules. Unfortunately, conjugated olefinic acids, e.g. cinnamic acid cannot be reduced under this procedure without involvement of the double bond.

Presumably, the carboxylic acid, on initial reaction with trifluoroacetic anhydride, forms a mixed anhydride (as shown by the IR spectroscopic data) which then undergoes facile reduction with zinc borohydride to give the corresponding alcohol. The details of the reaction course and the cause of

† Exceptionally, phenylacetic acid is reduced smoothly to 2-phenylethanol over 24 h.

**Table 1** Reduction of carboxylic acids ( $\text{RCO}_2\text{H}$ ) to the corresponding alcohols ( $\text{ROH}$ ) with  $\text{Zn}(\text{BH}_4)_2$  in DME in the presence of TFA

Entry	Carboxylic acids, R	t/h	Alcohols, R	Yield (%) <sup>a</sup>
1	$\text{CH}_3(\text{CH}_2)_6$	24	$\text{CH}_3(\text{CH}_2)_7$	90
2	$\text{CH}_3(\text{CH}_2)_{10}$	24	$\text{CH}_3(\text{CH}_2)_{11}$	85
3	$\text{CH}_3(\text{CH}_2)_{16}$	24	$\text{CH}_3(\text{CH}_2)_{17}$	92
4	$\text{PhCH}_2$	24	$\text{C}_6\text{H}_5(\text{CH}_2)_2^b$	90
5	$\text{Ph}(\text{CH}_2)_2$	48	$\text{C}_6\text{H}_5(\text{CH}_2)_3$	80
6	$\text{Ph}_2\text{CH}$	48	$\text{Ph}_2\text{CHCH}_2$	50 <sup>c</sup>
7	$\text{CH}_3(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_7$	24	$\text{CH}_3(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_8$	91
8	Ph	48	$\text{PhCH}_2$	55 <sup>c</sup>
9	<i>p</i> - $\text{Cl-C}_6\text{H}_4$	48	<i>p</i> - $\text{Cl-C}_6\text{H}_4\text{CH}_2$	75 <sup>c</sup>
10	<i>p</i> - $\text{NO}_2\text{C}_6\text{H}_4$	48	<i>p</i> - $\text{NO}_2\text{-C}_6\text{H}_4\text{CH}_2$	60 <sup>c</sup>
11	<i>o</i> - $\text{C}_6\text{H}_4(\text{CO}_2\text{H})_2$	48	<i>o</i> - $\text{C}_6\text{H}_4(\text{CH}_2\text{OH})_2$	62 <sup>c</sup>
12	<i>o</i> -Carboxymethylbenzoic acid	24	3,4-Dihydroisocoumarin <sup>d</sup>	80
13	$\text{C}_6\text{H}_{11}\text{CO}_2\text{H}$	24	$\text{C}_6\text{H}_{11}\text{CH}_2\text{OH}$	90
14	$\text{CH}_3(\text{CH}_2)_{16}\text{CO}_2\text{Me}$	24	No reaction	

<sup>a</sup> The yield was calculated on the basis of the isolated pure products. <sup>b</sup> The reduction was carried out without TFA. <sup>c</sup> The remainder was recovered carboxylic acid. <sup>d</sup> The mode of lactone formation is described in the text.

acceleration are under investigation and will be reported in due course.

In conclusion, the present procedure using a zinc borohydride-TFA reagent system provides an efficient reduction of a carboxylic acid to an alcohol through a mild and simple operation. This methodology is general and safe for the selective reduction of carboxylic acids in the presence of a number of sensitive functional groups. We believe, this procedure will certainly find suitable and significant application in the field of organic synthesis.

### Experimental

*General Procedure.*—The carboxylic acid (1 mmol) was stirred with trifluoroacetic anhydride (1 mmol) at 0–5 °C (ice-water bath) for 15 min. A solution of zinc borohydride (4 mmol) in DME<sup>8</sup> (4 cm<sup>3</sup>) was then added and stirring was continued at that temperature and then at room temperature for a certain period of time as indicated in Table 1. The reaction mixture was then decomposed with careful dropwise addition of water and subsequently filtered. The residue was washed with diethyl ether and the combined washings and filtrate were extracted with diethyl ether (3 × 10 cm<sup>3</sup>). The diethyl ether extract was washed with aqueous sodium hydrogen carbonate solution, brine, and dried (Na<sub>2</sub>SO<sub>4</sub>). Evaporation of the solvent afforded the practically pure alcohol which was further purified by column chromatography over silica gel. The alcohols are all known compounds and are easily identified by comparison of their spectra.

Although the procedure was described in 1 mmol scale, gram-scale reactions were carried out and found to afford the corresponding alcohols in similarly good yields.

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