

## UNUSUAL REACTIVITY OF ZINC BOROHYDRIDE - REDUCTION OF AMIDES TO AMINES

S. Narasimhan,\* S. Madhavan, R. Balakumar & S. Swarnalakshmi

Centre for Agrochemical Research, SPIC Science Foundation, Guindy, Madras 600 032.

**Abstract :** Zinc borohydride reduces secondary amides to the corresponding N-ethyl amines in excellent yields. The reduction requires only stoichiometric quantities of hydride and does not require the addition of any Lewis acid. The amides are isolated by simple hydrolysis of the reaction mixture.

Reduction of amides can lead to the formation of aldehydes/alcohols by the cleavage of C-N bond or amines by the cleavage of C-O bond. All the three product types have been observed when boron reagents have been employed as reducing agent. The type of product formed depends largely on the type of boron reagent employed and on the nature of the amide (whether primary, secondary or tertiary). For example, reaction of all the three types of amide with borane results in the formation of amine.<sup>1</sup> While reduction with more hindered hydride transfer reagents like, disiamyl borane produces aldehydes,<sup>2</sup> 9-BBN reduces secondary amides to the corresponding alcohols.<sup>3</sup> It has been shown that borane-THF and BMS are reagents of choice to reduce the three types of amides to the corresponding amines. An excess of one mole equivalent of borane is required to

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\* to whom all correspondence should be addressed

complex with the amine that is formed. However, the use of excess of borane can be avoided by using one equivalent of  $\text{BF}_3$  to the reaction mixture along with borane, since the latter is a stronger Lewis acid, it could preferentially complex with the amine.<sup>4</sup>

Alternatively, combination of metal borohydride and an acid has been used to effect this transformation. Thus,  $\text{NaBH}_4$  reduces amides in the presence of carboxylic acids<sup>5</sup>, sulfonic acids<sup>6</sup> and Lewis acids.<sup>7</sup> In another indirect approach the amide is converted to imino ether or to the alkoxyiminium salt rendering this substrate more susceptible to attack by a nucleophilic borohydride.<sup>8</sup> Reduction using "Super Hydrides" results in the formation of alcohols. However, only tertiary amides can be reduced while primary and secondary amides are not affected.<sup>9</sup>

Studies on zinc borohydride ( $\text{Zn}(\text{BH}_4)_2$ ) has revealed the fact that it possesses 'borane like' character and reduces carboxylic acids and amino acids to the corresponding alcohols.<sup>10, 11</sup> This is in contrast to metal borohydrides. Being neutral in nature,  $\text{Zn}(\text{BH}_4)_2$  can be utilized for the reduction of amides with only stoichiometric quantities of hydride. Indeed, the study has revealed that the reagent effects only C-O cleavage and results in the formation of the corresponding amines utilizing only stoichiometric quantities of hydride.

Typically, during the reduction of acetanilide by  $\text{Zn}(\text{BH}_4)_2$ , one equivalent of hydrogen was evolved and further reaction resulted in the complete reduction to afford the amine. The product was isolated by simple hydrolysis of the reaction mixture. Several amides were reduced by this method, utilizing only stoichiometric quantities of hydride (3equiv. per amide). The results are presented in Table 1.

Interestingly, presence of substituents in the aryl group influenced the rate of reduction. Thus, o-nitro acetanilide was reduced only to the extent of 30% even after 7 h, presumably due to pronounced ortho effect. However, reduction of the methyl ester of anthranilic acid afforded the corresponding amino alcohol. Other reducible groups like chloro, bromo, etc., were unaffected.

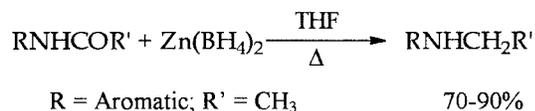


Table 1. Reduction of anilides by Zinc Borohydride

Substrate	Time (h)	Product	Yield (%)
Acetanilide	5	N-ethylaniline	90
3-Chloro acetanilide	4	N-ethyl 3-chloroaniline	85
4-Chloro acetanilide	4	N-ethyl 4-chloroaniline	85
4-Bromo acetanilide	4	N-ethyl 4-bromoaniline	85
4-Methoxy acetanilide	6	N-ethyl 4-methoxyaniline	70
2-Nitro acetanilide	8	N-ethyl 2-nitroaniline	30 <sup>a</sup>
3,4-Dichloro acetanilide	5	N-ethyl 3,4-dichloroaniline	80
4-Bromo-3-chloro acetanilide	5	N-ethyl 4-bromo-3-chloroaniline	75
Benzanilide	7	N-benzylaniline	70
Carbomethoxy acetanilide	3	o-(N-ethyl)aminobenzyl alcohol	80

<sup>a</sup> 70% of unreacted amide was recovered

The method offers a simple and convenient procedure to prepare N-ethyl anilines.

### Experimental Section

Reduction of acetanilide is representative: To 0.65 g (5 mmol) of acetanilide, 6.25 mL of Zn(BH<sub>4</sub>)<sub>2</sub> (0.36 M, 2.3 mmol) in THF was added and refluxed for 4 h. Any

excess hydride present was quenched with 1 mL of H<sub>2</sub>O. The mixture was saturated with K<sub>2</sub>CO<sub>3</sub> and the supernatant layer was filtered and dried over K<sub>2</sub>CO<sub>3</sub>. The solvent was removed to yield 0.54 g of N-ethylaniline (90%) .

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