

## A Novel and Chemoselective Protocol for the Reduction of Azides Using FeCl<sub>3</sub>-Zn System

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Chemoselective reduction of alkyl, aryl, aroyl and arylsulfonyl azides to the parent amines or amides, respectively, occurs in excellent yields upon treatment with a novel inexpensive reduction system consisting of FeCl<sub>3</sub>-Zn at room temperature.

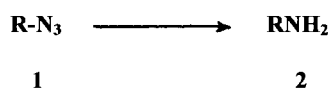
Reduction of azides to amines is an important reaction in organic synthesis, especially in carbohydrate and nucleoside chemistry.<sup>1</sup> A number of methods have been reported<sup>2</sup> for this reductive process describing the use of, for example, lithium aluminium hydride,<sup>3</sup> catalytic hydrogenation<sup>2</sup>, zinc borohydride,<sup>4</sup> borohydride exchange resin (BER)-nickel acetate,<sup>5</sup> lithium aminoborohydrides,<sup>6</sup> sodium borohydride,<sup>7</sup> benzyl triethylammonium tetrathiomolybdate<sup>8</sup> and bakers' yeast<sup>9</sup> etc. But most of these methods have one or more drawbacks with regard to general applicability, selectivity, ready availability, operational convenience or toxicity. For instance, LiAlH<sub>4</sub> is not tolerable to many functionalities, such as -COOR, -NO<sub>2</sub> etc. and on the other hand, catalytic hydrogenation and diborane reduction have limitations for being applied to unsaturated compounds containing a double or a triple bond. Also sodium borohydride does not usually convert azides to amines in good yield at ambient conditions in homogeneous systems, except in the case of arylsulfonyl azides.<sup>10</sup> Recently reduction of azides by rare earths namely samarium iodide<sup>11</sup> and samarium<sup>12</sup> metals appeared in the literature. But the main drawbacks with these methods, the metals used were comparatively expensive and not readily available. As a result, there is always considerable interest in finding a simple and efficient reducing agent of general applicability to all types of azides with tolerance to other sensitive functionalities. Our interest in metal catalyst<sup>13</sup> prompted us to initiate systematic investigation on reduction of organic azides including aroyl, arylsulfonyl, aryl and alkyl azides. Herein we report a novel reduction system consisting of inexpensive FeCl<sub>3</sub>-Zn in ethanol for the chemoselective reduction of various organic azides. The reaction generally proceeded with excellent yields at room temperature. The main advantage of this new combination system over other methods is that

it exercises unique selectivity, is chemoselective, nonhazardous, readily available and inexpensive

In a typical case, to a mixture of ferric chloride (0.270 g, 1 mmol) and zinc powder (0.065 g, 1 mmol) in a round bottom flask was added a solution of phenyl azide (0.109 g, 1 mmol) in ethanol (25 mL) dropwise with constant stirring at 0 °C. It was then brought to room temperature and the stirring was continued for 4 h. (The progress of the reaction was monitored by tlc). After completion of the reaction, metal was filtered off and the filtrate was evaporated and extracted with chloroform (2 × 30 mL). The extract was washed with water and brine and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The organic layers were distilled off under reduced pressure to get the crude amine which was further purified by column chromatography using chloroform as eluent. Evaporation of the organic layers gave the corresponding crude aniline in virtually quantitative yield. Similar treatment of other organic azides gave the corresponding amines or amides in 80–98% yields.

The excellent yields of the reduction products demonstrate the efficiency of this new method. Table summarizes our results on the reduction of a number of aryl, alkyl, aroyl and arylsulfonyl azides. In all the reactions, the cleavage takes place between the N-N bond, rather than the C-N or S-N bond. At the same time, azides are selectively reduced in the presence of a double bond (entries 11 and 12), an aromatic methoxyl group, acetonide and carboxyl groups. In case of nitro substituted aromatic azides, the corresponding nitro aniline was selectively obtained without any further reduction of nitro group (entry 4). Furthermore, haloaromatic azides showed remarkable selectivity to give the amine without any dehalogenation (entries 2, 3 and 7). Also the amides are not reduced further to the corresponding amines. In addition, it was worth commenting that 4-acetylphenylazide was converted to the 4-aminoacetophenone and the sensitive carbonyl group remains intact. Similar to aryl azides, *p*-toluenesulfonylazide also undergoes fast and clean reduction with this novel reduction system. The use of a lesser amount of the reagent normally results in significant recovery of the starting azide. To include an example of aliphatic azide we have carried out the reduction of 1-hexyl azide under same conditions and the corresponding 1-hexylamine was obtained in 80% yield (entry 9).



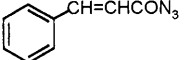
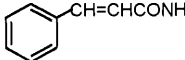
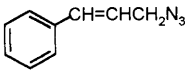
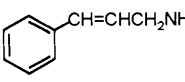
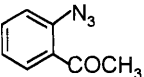
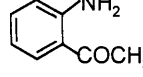
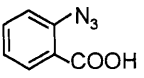
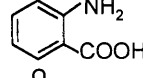
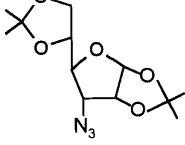
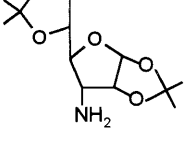
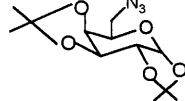
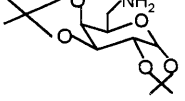
In conclusion, the present results demonstrate the novelty of zinc-ferric chloride combination system which shows unique selectivity and constitute a useful alternative to the commonly accepted procedure for the synthesis of various primary amines or amides. Moreover, this simple, readily available and cheap metal affords various amines or amides in excellent yields without the formation of any undesirable side products than the classical methods.



R = Aryl, Alkyl, Aroyl, Arylsulfonyl

**Scheme 1**

**Table 1:** Reduction of azides with FeCl<sub>3</sub>-Zn system

Entry	Azides	Amine/Amides <sup>a</sup>	Reaction time/h	Yield <sup>b</sup> %
1	C <sub>6</sub> H <sub>5</sub> N <sub>3</sub>	C <sub>6</sub> H <sub>5</sub> NH <sub>2</sub>	4	98
2	4-ClC <sub>6</sub> H <sub>4</sub> N <sub>3</sub>	4-ClC <sub>6</sub> H <sub>4</sub> NH <sub>2</sub>	5	90
3	3-ClC <sub>6</sub> H <sub>4</sub> N <sub>3</sub>	3-ClC <sub>6</sub> H <sub>4</sub> NH <sub>2</sub>	4	87
4	2-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> N <sub>3</sub>	2-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> NH <sub>2</sub>	4.5	80
5	4-MeOC <sub>6</sub> H <sub>4</sub> N <sub>3</sub>	4-MeOC <sub>6</sub> H <sub>4</sub> NH <sub>2</sub>	4	86
6	4-MeCOC <sub>6</sub> H <sub>4</sub> N <sub>3</sub>	4-MeCOC <sub>6</sub> H <sub>4</sub> NH <sub>2</sub>	5	83
7	4-BrC <sub>6</sub> H <sub>4</sub> N <sub>3</sub>	4-BrC <sub>6</sub> H <sub>4</sub> NH <sub>2</sub>	4	90
8	4-MeC <sub>6</sub> H <sub>4</sub> CON <sub>3</sub>	4-MeC <sub>6</sub> H <sub>4</sub> CONH <sub>2</sub>	4	80
9	Me-CH <sub>2</sub> (CH <sub>2</sub> ) <sub>6</sub> -N <sub>3</sub>	Me-CH <sub>2</sub> (CH <sub>2</sub> ) <sub>6</sub> -NH <sub>2</sub>	4	80
10			5	81
11			4.5	86
12			4.5	90
13	C <sub>6</sub> H <sub>5</sub> SO <sub>2</sub> N <sub>3</sub>	C <sub>6</sub> H <sub>5</sub> SO <sub>2</sub> NH <sub>2</sub>	4	82
14	4-MeC <sub>6</sub> H <sub>4</sub> SO <sub>2</sub> N <sub>3</sub>	4-MeC <sub>6</sub> H <sub>4</sub> SO <sub>2</sub> NH <sub>2</sub>	4.5	81
15			5	85
16			6	80
17			6	82
18			6	80

<sup>a</sup>Amines identified by spectral comparison with authentic samples available commercially or independently prepared. <sup>b</sup>All the yields refer to isolated chromatographically pure compounds.

**References**

- C. Grundmann, "Methods der Organischen Chemie," 4th ed., ed. by E. Miller, Houben-Weyl, Georg Thieme Verlag, Stuttgart, (1965), Vol 10/3, pp. 822; R. Schroter, "Methoden der Organischen Chemie," 4th ed., ed. by E. Miller, Houben-Weyl, Georg Thieme Verlag, Stuttgart, (1957), Vol 11/1, pp. 539; T. Sheradsky, "The Chemistry of the Azido Group", ed. by S. Patai, Interscience Publishers, New York, (1971), Chap. 6.
- E. F. V. Scrivan and K. Turnbull, *Chem. Rev.*, **88**, 298 (1988).
- J. H. Boyer, *J. Am. Chem. Soc.*, **73**, 5865 (1951).
- B. C. Ranu, A. Sarkar, and R. Chakraborty, *J. Org. Chem.*, **59**, 4114 (1994).
- N. M. Yoom, J. Choi, and Y. S. Shon, *Synth. Commun.*, **23**, 3047 (1993).
- S. G. Alvarez, G. B. Fisher, and B. Singavam, *Tetrahedron Lett.*, **36**, 2567 (1995).
- P. A. S. Smith, J. H. Hall, and R. O. Kan, *J. Am. Chem. Soc.*, **84**, 485 (1962); T. Gastiser, C. Selve, J. J. Delpucch, *Tetrahedron Lett.*, **24**, 1609 (1983).
- A. R. Ramesha, S. Bhat, and S. Chandrasekan, *J. Org. Chem.*, **60**, 7682 (1995).
- M. Baruah, A. Boruah, D. Prajapati, and J. S. Sandhu, *Synlett*, **1996**, 1193.
- M. Hadayatullah, and A. Guy, *Synthesis*, **1978**, 357.
- L. Benati, P. C. Montevecchi, D. Nanni, P. Spagnolo, and M. Volta, *Tetrahedron Lett.*, **36**, 7313 (1995); C. G. Dubois, and M. Hesse, *Tetrahedron Lett.*, **36**, 7427 (1995).
- Y. Huang, Y. Zhang, and Y. Wang, *Tetrahedron Lett.*, **38**, 1065 (1997).
- B. Baruah, A. Boruah, D. Prajapati, and J. S. Sandhu, *Tetrahedron Lett.*, **38**, 1449 (1997); A. Boruah, B. Baruah, D. Prajapati, and J. S. Sandhu, *Tetrahedron Lett.*, **38**, 4267 (1997).