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Reduction of Azides to Amines with New Metal /Lewis Acid Systems in H_2O or Aqueous EtOH

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Abstract: The azides were reduced to the corresponding amines by two new metal/Lewis acid systems in water or in aqueous EtOH in yields ranging from 80%-95%. The reaction rates were faster in water than in aqueous EtOH in most cases. All 16 azides with different functional groups were well reduced to the corresponding amines in excellent yields and reaction rates.

Keywords: Azides, reduction, metals, Lewis acids.

Azides[1] can be reduced to amines by various reagents, such as LiAlH$_4$[2], H$_2$/Lindlar catalyst[3], PPh$_3$[4], NaBH$_4$/PTC[5], Mg and Ca/MeOH[6] *etc*.. More recently, SmI$_2$[7], Fe/NiCl$_2$.6H$_2$O-THF[8], H$_2$N-NMe$_2$/FeCl$_3$.6H$_2$O[9], MCM-Silylamine Pd(II)complex[10], AlI$_3$[11], In/NH$_4$Cl[12] Sm/CoCl$_2$.6H$_2$O[13] were also reported to perform this transformation well. In most of the cases, volatile organic solvents were used as reaction media. While for environmental reasons, water would be a more preferred one. Additionally, water-based media usually have the advantages of rate enhancement, chemoselectivity and stereoselectivity improvement[14].

In this paper, two new systems (Zn/AlCl$_3$, Zn/BiCl$_3$), which are capable of reducing azides to amines efficiently in water or in aqueous ethanol, are reported. The reaction yields were both excellent in water and in aqueous EtOH, while the reaction rates in water were almost twice faster than those in aqueous ethanol in most of the cases. It is worthy noting that these metals and Lewis acids are non-toxic and inexpensive, and the operation was very simple. One of the two systems, Zn/BiCl$_3$ in H$_2$O/EtOH (2:1) was further used for other 12 more cases. It was found that these reduction reactions were performed very well and showed excellent chemoselectivities in the presence of halo (**4**, **10**, **Table 1**), carbonyl (**11**), carboxy (**12**), nitro (**13**), sulfonyl (**16**) groups or unsaturated double bond (**15**) in the substrates.

$$RN_3 \xrightarrow[H_2O \text{ or } H_2O/EtOH]{\text{Lewis acid/Metal}} RNH_2$$

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Table 1 Results of reduction of azides to the corresponding amines in water or aq. EtOH

azides	Reducing agents[a]	Yield(%)[b]	Reducing agents[c]	Yield(%)[b]
1 R=Ph	Zn+$AlCl_3$(1)	85	Zn+$AlCl_3$(2)	89
	Zn+$BiCl_3$(2.5)	94	Zn+$BiCl_3$(2.5)	93
2 R=4-MeC_6H_4	Zn+$AlCl_3$(2)	83	Zn+$AlCl_3$(1.5)	83
	Zn+$BiCl_3$(1.5)	83	Zn+$BiCl_3$(1.5)	89
3 R=2-MeC_6H_4	Zn+$AlCl_3$(2)	85	Zn+$AlCl_3$(3)	83
	Zn+$BiCl_3$(1.5)	82	Zn+$BiCl_3$(2.5)	89
4 R=4-BrC_6H_4	Zn+$AlCl_3$(2.5)	81	Zn+$AlCl_3$(2.5)	89
	Zn+$BiCl_3$(2)	80	Zn+$BiCl_3$(2)	85
5 R=n-$C_{12}H_{25}$			Zn+$BiCl_3$(3)	83
6 R=c-C_6H_{11}			Zn+$BiCl_3$(3.5)	81
7 R=$PhCH_2$			Zn+$BiCl_3$(2.5)	89
8 R=2,6-$Me_2C_6H_3$			Zn+$BiCl_3$(2.5)	85
9 R=4-$MeOC_6H_4$			Zn+$BiCl_3$(3.5)	90
10 R=4-ClC_6H_4			Zn+$BiCl_3$(2.5)	94
11 R=$PhCOCH_2$			Zn+$BiCl_3$(2)	91
12 R=2-$HOOCC_6H_4$			Zn+$BiCl_3$(3.5)	86
13 R=2-$NO_2C_6H_4$			Zn+$BiCl_3$(3)	84
14 R=C_6H_5CO			Zn+$BiCl_3$(1)	87
15 R=$C_6H_5CHCHCO$			Zn+$BiCl_3$(1)	85
16 R=4-$MeC_6H_4SO_2$			Zn+$BiCl_3$(1.5)	84

a) in water; time in hour in parentheses. b) isolated yield. c) in aq. alcohol; time in hour in parentheses.

The reason for the rate difference between the media is probably due to that the acceleration of electron transfer from metals to Lewis acids complexed azides is stronger in water than that in aqueous ethanol. Detailed mechanism and more applications of these methods are under investigation in this laboratory.

In conclusion, we have demonstrated the efficiency of the two new metal/Lewis acids as reductants for azides transformation to amines. It is especially of interests to note that these reactions could be conducted in water or aqueous EtOH in excellent yields with higher chemoselectivity and reaction rates.

Typical procedure: To a stirred mixture of zinc power (1.30 g, 0.02 mol), $AlCl_3.6H_2O$ (4.83 g, 0.02 mol) and water (20 mL) in round bottom flask was added dropwise a solution of phenyl azide (1.19 g, 0.01 mol) in EtOH (2 mL). The reaction mixture was stirred for 2 h, until the reaction was completed (monitored by TLC). Aqueous NaOH (20 mL, 10%) was added and the whole mixture was stirred at room temperature for 5 min. The deposit was filtered off and washed with ethyl acetate (10 mL). The filtrate was concentrated and extracted with ethyl acetate (25 mL×3). The combined extracts were washed with water, brine and dried over anhydrous Na_2SO_4. The solvent was removed in vacuum, the residue was purified by column chromatography using ether-petroleum ether (1:4) as eluent to offered the pure product (0.79 g, 89%), which was confirmed by spectroscopic methods.

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