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REDUCTION OF AZIDES TO AMINES OR AMIDES WITH ZINC AND AMMONIUM CHLORIDE AS REDUCING AGENT

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ABSTRACT

Alkyl azides and acyl azides were reduced to the corresponding amines and amides with zinc and ammonium chloride as reducing agent under mild conditions in good to excellent yield.

It is widely known that most of primary amines are biologically active compounds or the important building blocks for the syntheses of biologically active compounds, such as aminobenzlactam **1**,[1] aminobenzlactam **2**,[2] and L-homophenylalanine **3**,[1a,3] and so on. The reduction of azides to amines is of considerable importance for the introduction of primary amino group in organic synthesis because of the easy preparation of azide by regio and

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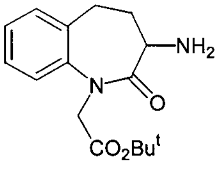
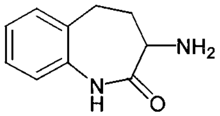
stereo controlled procedure.[4] Many common reagents for this purpose have been developed,[5] but some of them suffer from poor selectivity[4] or using some environmentally unfriendly chemicals.[6] The use of zinc and ammonium chloride has been well established in organic synthesis for the reduction of nitro group,[7] however, little attention has been focused on the reduction of azido group.[8] Herein, we will describe a facile method for the reduction of azides to amines or amides in good to excellent yield using zinc and ammonium chloride as reducing agent under mild condition.



1



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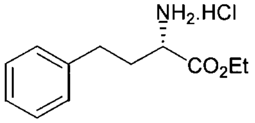

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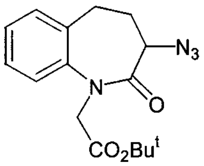

4

Aminobenzlactam **1**, a key intermediate for the synthesis of many biologically active compounds,[1] such as thromboxane synthase inhibitors, and benazepril hydrochloride, can be prepared by reduction of the corresponding azide **4**. Initially, we tried to reduce **4** via hydrogenation over 10% and 5% palladium on carbon at room temperature under 1, 5 and 10 atmospheric hydrogen, a general method for the reduction of azides,[4] but the yields were always below 54% due to the incomplete conversion (Table 1, Entry 1). Hydrogen transfer reduction was tested for this transformation with ammonium formate as hydrogen donor,[9] in the presence of 10% palladium on carbon, but the reaction could not proceed completely, either, and only 43% yield was isolated (Table 1, Entry 2). Using 5% palladium on aluminum as catalyst and ammonium formate as hydrogen donor, resulted in more than 65% yield (Table 1, Entry 3). The combination of sodium borohydride and cobalt chloride, which was very efficient for the reduction of azides,[5b] was also employed to reduce **4**, but low yield of 45% was obtained (Table 1, Entry 4). The treatment of

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Table 1. Reduction of Azide **4** to Amine **1** with Various Reducing Agents

Entry	Reducing Agent	Temperature	Time	Isolated Yield (%)
1	H_2-10%Pd/C	rt	8–24 h*	<54
2	HCO_2NH_4-10%Pd/C	rt	24 h	43
3	HCO_2NH_4-5%Pd/Al	rt	24 h	65
4	$NaBH_4/CoCl_2 \cdot 6H_2O$	rt	24 h	45
5	Fe/NH_4Cl	reflux	1 h	73
6	Zn/NH_4Cl	reflux	10 min	90

*The hydrogenation of **4** to **1** were carried out under 1, 5, 10 atmospheric hydrogen in EtOH and THF.

ferrum and ammonium chloride with **4** led to much higher yield of 73% (Table 1, Entry 5).[10] However the conversion was still not complete even if the reaction was prolonged.

Considering zinc is more reactive than ferrum, we proposed that the combination of zinc and ammonium chloride was probably more efficient for the reduction of azides than that of ferrum and ammonium chloride. As we expected, the azide **4** was reduced to amine completely in a short time to provide 90% isolated yield (Table 1, Entry 6). The co-solvents of ethyl acetate and water, ethyl alcohol and water as well as ethyl acetate, ethanol and water were suitable for the reaction, which could be selected based on the solubility of azides.

To extend the scope of the reducing reagent of zinc and ammonium chloride for the reduction of other azides, a variety of azides prepared according to the literature[4,11] were tested for this transformation (Table 2). All of azides were reduced completely with zinc and ammonium chloride at refluxing or room temperature to readily give the corresponding amines or amides in good to excellent yields. Moreover, this new reduction system of zinc and ammonium chlorides could tolerate some functional groups which were easily destroyed during hydrogenation, such as C=C bond, benzyl, and so on, thus the azides bearing such groups were reduced in high yields (Entries 2 and 4). The reductions of Aroyl azide, arylsulphonyl azides were performed at room temperature to afford the corresponding amides smoothly in over 94% yields (Entries 5 and 6). Aryl azide was also reduced in excellent yield (98%, Entry 7). For the reduction of the optically active azide, no racemization was observed (Entry 8).

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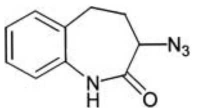
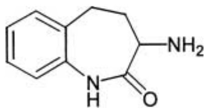
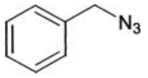
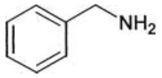
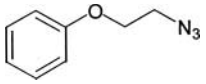
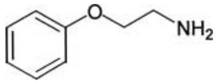
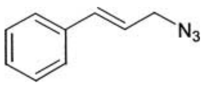
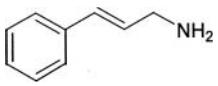
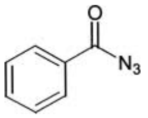
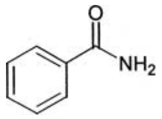
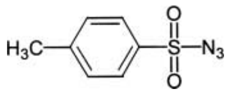
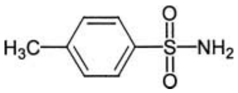
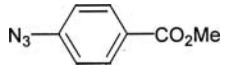
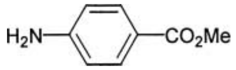
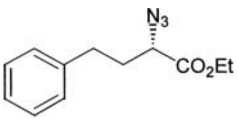
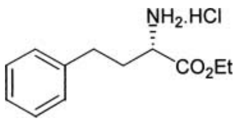
Table 2. Reduction of Azides to Amines or Amides with Zn/NH_4Cl in EtOH/H_2O (3 : 1)

Entry	Azides	Product	Temperature	Time (min)	Yield (%)
1			reflux	10	98
2			reflux	10	87
3			reflux	10	96
4			reflux	10	86
5			rt	120	94
6			rt	120	95
7			reflux	30	98
8			reflux	10	87

*Yield of isolated product.

In summary, using zinc and ammonium chloride to reduce a broad spectrum of azides to amines or amides in good to excellent yields was first presented, which might provide a facile alternative for the reduction of azides to amines and amides under a mild condition.

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EXPERIMENT

Typical Experiment Procedure for the Reduction of Azides to Amines and Amides with Zinc and Ammonium Chloride

To the solution of azides (0.03 mol) and ammonium chloride (0.07 mol) in ethyl alcohol (80 mL) and water (27 mL), zinc powder (0.04 mol) was added, the mixture was stirred vigorously at room temperature or at refluxing. After the reaction is over (monitored by TLC), ethyl acetate (200 mL) and aqueous ammonia (10 mL) was added. The mixture was filtered, and the filtrate was washed with brine, dried over anhydrous sodium sulfate. After removal of solvent under reduced pressure, the residue was purified by a flash chromatography or recrystallization to give the corresponding amines or amides.

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