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Zn/NH_4Cl: A facile and efficient reagent system for reduction of organic halides

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ABSTRACT

A simple and efficient method of zinc dust/ammonium chloride system for the reductive dehalogenation of alkyl halides has been described. The reaction is carried out under mild conditions. The significant feature of this method is the isolation of the pure product by simple work up in a short time.

KEYWORDS

Zinc dust;
Organic halides;
Dehalogenation;
Reduction.

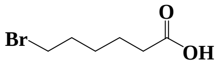
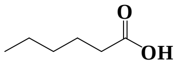
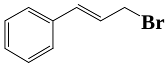
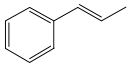
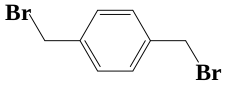
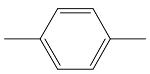
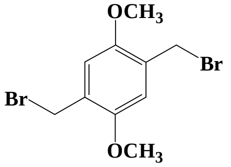
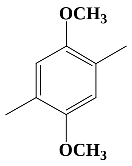
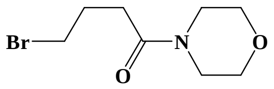
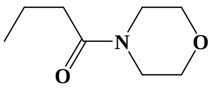
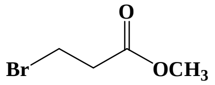
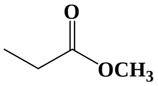
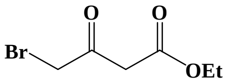
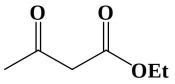
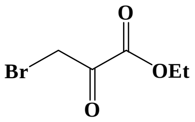
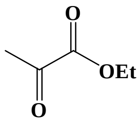
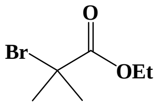
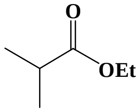
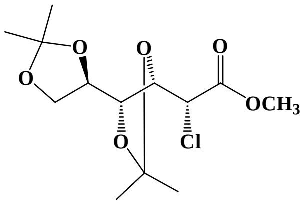
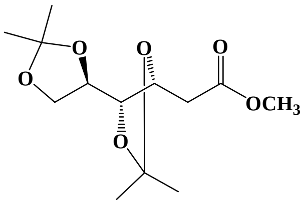
INTRODUCTION

The reductive dehalogenation of alkyl halides is an useful transformation in the synthesis of numerous organic compounds and also in the synthesis of key intermediates of important pharmaceutical compounds. Earlier reports revealed that the reductive dehalogenation has been achieved by the systems like Bu_3SnH with a catalytic amount of AIBN[1], organolanthanide hydride/NaH[2], Cp_2TiBH_4[3] and $[Cp_2TinBu_2]^-MgCl^+$[4]. These systems require reaction time as long as 5–10 hrs at reflux, expensive catalysts are used but offer very low yield. Moreover, stringent precautions must be taken while employing Bu_3SnH because of its toxic nature and also has limitations based on chemoselectivity and economic considerations. Therefore, there is a need of an efficient and inexpensive non toxic reagent system for the reductive dehalogenation of alkyl halides. Recently, we have also developed a new protocol for the synthesis of optically pure methyl-D-erythro-2,3-dihydroxy butanoate, using environmentally benign zinc dust/NH_4Cl reagent system for reductive debromination as a key step[5].

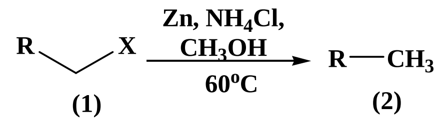
In continuation of our work to develop new methodology for organic transformations, we herein report that zinc dust/NH_4Cl reagent system might be an useful and inexpensive non toxic reagent for the reduction of terminal alkyl halides. Though zinc has been extensively used in the preparation of organometallic compounds[6] and as a reducing agent[7] in organic synthesis, the utility of zinc for the synthesis of α,β-unsaturated ketones by a reaction of an acid chloride with allyl bromide[8] and homoallylic alcohols[9] has also been demonstrated. Furthermore, the zinc mediated preparation of triphenyl phosphonium ylides[10], Fridel-Crafts acylation[11] and carbamate formation[12] has been reported. In this context, the use of zinc as a reagent in the organic synthetic processes has gained considerable importance due to promoting and catalyzing organic transformations under ambient conditions, without the need for any added catalyst or ligand.

In this letter, we report a rapid and efficient reduction of halides to corresponding reduced products using zinc dust and ammonium chloride at 60^0C in metha-

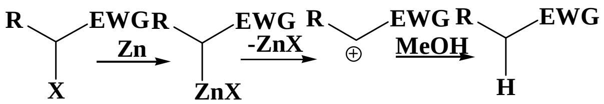
TABLE 1: Reduction of organic halides using zinc and NH_4Cl in methanol

Entry	Substrate(1a-j)	Product(2a-j)	Reaction conditions	Yield (%)[a]
1			60^{0}C, 4 h	72
2			60^{0}C, 3 h	70
3			60^{0}C, 3 h	76
4			60^{0}C, 3 h	78
5			60^{0}C, 4 h	70
6			60^{0}C, 4 h	68
7			rt, 3 h	75
8			rt, 4 h	78
9			rt, 4 h	70
10			rt, 3 h	73

[a]Yields refer to pure isolated products and were characterized by spectral data.



SCHEME 1



SCHEME 2

nol as depicted in SCHEME 1. Various other functionalities like –OH, –OCH_3, –COOR, > C = C < and –CH_3 are tolerated (TABLE 1).

RESULTS AND DISCUSSION

The reduction of terminal halides in the presence of zinc dust and ammonium chloride was completed within three to four hours. The course of reaction was monitored by TLC. The work-up and isolation of the products were easy. Thus, the terminal halides reduced (a few examples are listed in TABLE 1) by this system were obtained in good to moderate yields (72-78%) and no undesired side product was observed[13]. The results shown in TABLE 1 clearly indicate the scope and generality of the reaction with respect to various alkyl halides. Allyl and benzyl halides, as well as α-halo carbonyl compounds are reduced by zinc/NH_4Cl.

The reductive elimination of halides from α-halo carbonyl compounds (TABLE 1; entry 7-10) consists an important example and to note that the reaction facilitated by the carbonyl group (EWG= electron-withdrawing group) for both elimination of ZnX and abstraction of proton from the methanol even at room temperature (SCHEME 2). It is a very good alternative for expensive Pd/C for these kinds of transformations[13].

Furthermore, the unactivated alkyl halides are reduced under these similar reaction conditions. The products were characterized by comparison of their boiling points or melting points, TLC and IR spectra with authentic samples. Further characterization of the products was done by ^{1}H and ^{13}C NMR spectroscopy.

In conclusion, we have demonstrated a very simple, efficient and practical method for the reductive dehalogenation using zinc dust with ammonium chloride. The important features of this method include (a) operational simplicity, (b) no need for any other additive to promote the reaction, (c) short reaction time, (d) the use of cheap, commercially available and non toxic reagents, and (e) good to moderate yields of desired products.

EXPERIMENTAL

^{1}H NMR spectra were recorded on 400 MHz Bruker AVANCE 400 spectrometer and ^{13}C NMR spectra were recorded on 100 MHz Bruker AVANCE 400 spectrometer, respectively using TMS as an internal standard. IR spectra were recorded on a Perkin-Elmer FT/IR 100 spectrometer. Mass spectra were recorded on Agilent-1100 mass spectrometer. All the reactions were monitored by thin layer chromatography (TLC). TLC was performed on F$_{254}$, 0.25 mm silica gel plates (Merck). Plates were eluted with appropriate solvent systems, and then stained with either alkali KMnO$_4$ or Ceric ammonium molybdate solutions prepared in the laboratory. The developed plates were first analysed under UV 254nm then stained with appropriate reagent. Column chromatography was performed using silica gel with particle size 100-200 mesh.

General procedure for preparation of (2a-j)

A solution of the starting substrate **(1a-j)** (1 mmol) in methanol (10 ml) was added ammonium chloride (0.5 mmol) and zinc dust (2 mmol). The mixture was stirred at 60^0C **(1a-f)** or room temperature **(1g-j)** for 3-4 hours. After the completion of the reaction (monitored by TLC), the reaction mixture was filtered through celite. The filtrate was evaporated under vacuum and the residue was taken into chloroform or ether (50 ml), washed twice with saturated brine solution and finally with water. The organic layer was dried over anhydrous sodium sulphate and evaporation of the organic layer was followed by column chromatographic purification to yield the desired products.

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