



Preparation and Characterization of Primary Amines by Potassium Borohydride-Copper Chloride System from Nitriles

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Nitriles undergo reduction to primary amines under optimized conditions at 50 °C using 0.25 equiv of copper chloride and 3.0 equiv of potassium borohydride in 80 % isopropanol. The aromatic and aralkyl nitriles could be effectively reduced in yield ranging from 60 to 90 %.

Keywords: Nitrile, Reduction, Potassium borohydride, Copper chloride.

INTRODUCTION

The prevalence and extensive use of amines as starting materials for plastics, agrochemicals and dyes in industry make it an important functional group in organic chemistry¹. The reduction of nitriles into the corresponding amines is a very important method, because of the ready commercial availability². There are a number of different methods for this conversion, including catalytic hydrogenation³, LiAlH₄ reduction⁴, sodium borohydride reduction⁵, etc.

As is known, sodium borohydride in combination with transition metal have been developed to reduce nitriles. In 1988 Itsuno *et al.*⁶ used NaBH₄-ZrCl₄ reducing nitriles and obtained good effect. The NaBH₄-CoCl₂ reagent system effectively reduces the nitriles in good yields in hydroxylic as well as non-hydroxylic solvents⁷. The halogenides, sulfates, carboxylates of nickel, iridium, rhodium, osmium and platinum were also used along with NaBH₄ in several applications⁸. Sodium borohydride-I₂ can also reduce nitriles⁹.

Interestingly, potassium borohydride-metal salt system also has the similar role, even though the reducing power of potassium borohydride is rather limited. Here, we would like to report a simple and efficient reduction condition of potassium borohydride and readily available cupric salts. The reaction can be carried out in alcoholic solvents as well as in the mixture of alcoholic solvent and water which makes the work up process quite simple.

EXPERIMENTAL

All reagents are purchased without further purification. The ¹H NMR spectra was recorded in DMSO-*d*₆ on a Bruker 400 (400 MHz) spectrometer. The chemical shifts of ¹H NMR spectra are reported relative to TMS (δ 0.00) as the internal standard. GC was carried out with Agilent 6890N coupled with a FID detector using HP-5 column.

General procedure for the reduction of nitrile by KBH₄ and CuCl₂: To a 10 mL round-bottomed flask was added 2-(4-chlorophenyl)acetonitrile (0.15 g, 1 mmol), KBH₄ (0.17 g, 3 mmol), CuCl₂ (0.03 g, 0.25 mmol) and 80 % isopropanol (1.6 mL isopropanol and 0.4 mL water). The reaction completed in 8 h at 60 °C as evidenced by TLC (DCM:MeOH 10:1). The reaction mixture was cooled to 25 °C and removed the solvent. Ethyl acetate (5 mL) was added to the residue, washed with water (1 mL) and brine (1 mL). The organic layer were dried with anhydrous Na₂SO₄, filtered and evaporated *in vacuo* to afford the crude product. The crude product was determined by GC.

2-(4-Chlorophenyl)ethanamine (Table-3, entry 1): Yellowish oil, 90 % yield, ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.68 (s, 2H), 3.19 (m, 2H), 7.24 (d, 2H), 7.34 (d, 2H); APCI-MS: found *m/z* 156.00.

2-(3-Chlorophenyl)ethanamine (Table-3, entry 2): Yellowish oil, 78 % yield, ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.77 (s, 2H), 1.89 (m, 2H), 2.75 (m, 2H) 7.24 (m, 4H); APCI-MS: found *m/z* 156.02.

2-(4-Methoxyphenyl)ethanamine (Table-3, entry 4): Yellowish oil, 80 % yield; $^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ 2.66 (m, 2H), 2.91 (m, 2H), 3.72 (s, 3H), 6.85 (d, 2H), 7.12 (d, 2H); APCI-MS: found m/z 151.92.

Phenethylamine (Table-3, entry 5): Yellowish oil, 60 % yield, $^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ 2.64 (t, 2H, $J = 6.4$), 2.80 (t, 2H, $J = 6.4$), 7.18-7.29 (m, 5H); APCI-MS: found m/z 122.12.

Benzylamine (Table-3, entry 6): Yellowish oil, 87 % yield, $^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ 2.64 (t, 2H), 2.80 (t, 2H), 7.18-7.29 (m, 5H); APCI-MS: found m/z 108.11.

4-Methoxybenzylamine (Table-3, entry 8): Yellowish oil, 83 % yield, $^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ 3.66 (s, 2H), 3.72 (s, 3H), 6.87 (d, 2H), 7.21 (d, 2H); APCI-MS: found m/z 139.13.

2-(3-Fluorophenyl)ethanamine (Table-3, entry 9): Yellowish oil, 73 % yield, $^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ 2.71 (m, 2H), 3.16 (m, 2H), 7.05 (m, 3H), 7.33 (dd, 1H); APCI-MS: found m/z 140.16.

RESULTS AND DISCUSSION

We have developed the method for reduction of nitriles with potassium borohydride and CuCl_2 . The initial studies were focused on the optimization of catalytic conditions based on 2-(4-chlorophenyl)acetonitrile as the model substrate. As shown in the Table-1, 2-(4-chlorophenyl)acetonitrile did not undergo reduction only with KBH_4 (Table-1, entry 1), but it was reduced with Cu^+ and Cu^{2+} catalysis (Table-1, entry 2-11). Additionally, the best result was obtained using CuCl_2 which gave a quantitative yield (Table-1, entry 2). If sodium borohydride took place of potassium borohydride, little product was obtained (Table-1, entry 12).

Entry	Agent	Yield ^b (%)
1	KBH_4	0
2	$\text{KBH}_4/\text{CuCl}_2$	90
3	KBH_4/CuBr	76
4	$\text{KBH}_4/\text{CuBr}_2$	73
5	KBH_4/CuO	65
6	$\text{KBH}_4/\text{CuO}_2$	82
7	$\text{KBH}_4/\text{CuF}_2$	43
8	$\text{Cu}(\text{OAc})_2$	56
9	KBH_4/CuI	31
10	$\text{KBH}_4/\text{CuSO}_4$	22
11	$\text{KBH}_4/\text{Copper acetylacetonate}$	30
12	$\text{NaBH}_4/\text{CuCl}_2$	< 10

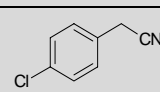
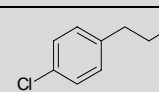
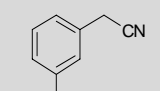
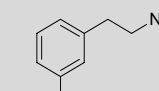
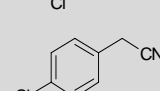
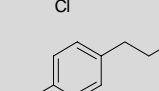
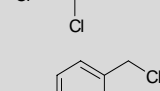
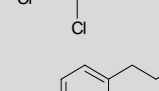
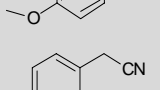
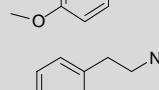
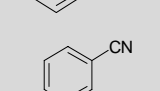
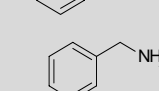
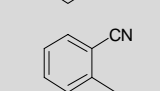
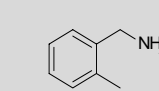
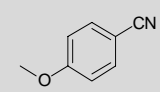
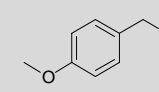
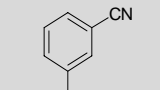
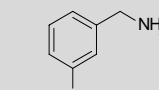
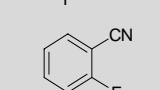
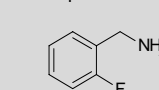
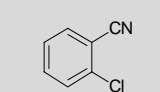
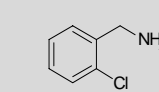
As shown in Table-2, several alcohols gave excellent results in this reduction. However, using methanol and ethanol lead to low yield and more formation of by-product (*sec*-amines¹⁰). 80 % Isopropanol is the solvent of choice and primary amines are obtained by simple procedure (Table-2, entry 6).


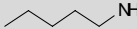
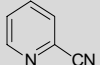
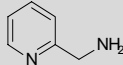
TABLE-2
EFFECT OF THE DIFFERENT SOLVENTS
TOWARDS THE REDUCTION OF NITRILES^a

Entry	Solvent	Yield ^b (%)	<i>sec</i> -Amines ^c (%)
1	MeOH	45 ^c	28
2	EtOH	63 ^c	22
3	95 % EtOH	75 ^{c,d}	13
4	Isopropanol	20	11
5	90 % Isopropanol	84 ^d	6
6	80 % Isopropanol	90 ^d	5

^aAll reactions were carried out by using 4-chloro-benzylcyanide (1.0 mL), KBH_4 (3 mmol), CuCl_2 (0.25 mmol) at 50 °C for 8 h; ^bDetermined by GC; ^cMore by-product was formed; ^dDiluted with water; ^eDetermined by GC, *sec*-amines were identified by MS

The optimized reaction conditions (0.25 mmol CuCl_2 , 3 mmol KBH_4 , 1.5 mL 80 % isopropanol) were used for the synthesis of a series of primary amines (Table-3).

Entry	Nitrile	Product	Time (h)	Yield ^b (%)
1			8	90
2			7	78
3			5	85
4			4	75
5			12	60 ^e
6			2	87
7			4	78
8			4	83
9			8	73
10			12	60
11			8	61

12			18	25 ^d
13			4	40 ^e

^aAll reactions were carried out by using nitriles (1.0 mL), KBH_4 (3 mmol), CuCl_2 (0.25 mmol) at 60 °C; ^bDetermined by GC, all products were identified by MS and ^1H NMR; ^c25 % nitrile was not reduced; ^d50 % nitrile was not reduced; ^eReaction in methanol

As shown in Table-3, the aromatic and aralkyl nitriles could be effectively reduced in yield ranging from 60 to 90 %. The reducing system was appropriate and convenient for phenyl acetonitrile derivatives and benzonitrile derivatives (Table-3, entries 1-11). However, KBH_4 - CuCl_2 is probably not effective to reduce long-chain aralkyl nitriles (Table-3, entry 12), about 50 % nitriles were not reduced. In the case of phenyl acetonitrile (Table-3, entry 5) low conversion was founded. Furthermore, the reducing system could also be applied for aromatic heterocyclic nitrile in methanol (Table-3, entry 13). But it had formed unidentified byproduct.

Conclusion

In summary, KBH_4 - CuCl_2 is simple, efficient, facile and convenient reducing agent for the reduction of nitriles into primary amines. Cupric chloride is proved to be a good and recyclable catalyst. The catalyst could be easily to get and use conveniently. A further advantage of present method is that it can be used with the compounds having functional groups like nitro groups, esters and ketones.

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