

Raney Ni/ KBH_4 : an efficient and mild system for the reduction of nitriles to amines

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Abstract

A new and efficient method of synthesizing primary amines from their corresponding nitriles with KBH_4 in dry ethanol catalyzed by Raney Ni has been discovered. It is proved that this route is so far the most facile, efficient and easy-to-handle method of reducing aliphatic and aromatic nitriles directly to primary amines. Under mild conditions, up to 93% isolated yields were achieved for aromatic or aliphatic nitriles. This approach opens up a new way for the utilization of potassium borohydride and the classical catalyst Raney Ni.

Keywords: Raney nickel, potassium borohydride, nitriles, amines, reduction

Introduction

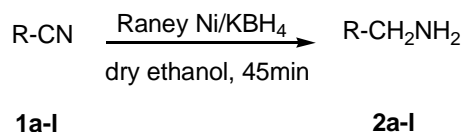
Nitrile hydrogenation is an important method to obtain amines. The most commonly used approaches in nitriles hydrogenation are using strong hydride donors, such as lithium aluminum hydride, or catalytic hydrogenation.¹ However, these methods always lack chemoselectivity and need complicated procedures to obtain target compounds. The difficulty arises because the imine, as an intermediate produced by the reduction of cyano group, could couple with an already formed primary amine, which leads to secondary amine. Furthermore, a secondary amine could also react with another imine molecule to form tertiary amine.² Therefore, transforming nitriles to primary amines with high selectivity and yields has become an important field to chemists.^{3,5,6,7,12,13} Except for a few examples,⁴ KBH_4 or NaBH_4 alone generally could not reduce nitriles to amines.^{1a,5} The reducing ability of NaBH_4 could be enhanced by introducing some

special additives. For example, CoCl_2 , ZrCl_4 , I_2 and bis(2-bromoethyl)selenium dibromide ⁶ are effective additives for the reaction. Recently Khurana et al ⁷ reported that aromatic nitriles could be reduced to primary amines with NaBH_4 using NiCl_2 as additive. However, this method is not efficient for aliphatic nitriles. Caddick and co-workers ⁸ introduced a suitable trapping agent such as acetic anhydride or di-*tert*-butyl dicarbonate to the reaction ($\text{NiCl}_2/\text{NaBH}_4$), the protected primary amines were firstly obtained, and the product amines were formed by subsequent deprotection treatment. In this method, longer synthesis routes were needed and the yields of primary amines are not high enough.

KBH_4 is usually used to react with metal salts to prepare metal borides ⁹ that are used as the catalysts in catalytic hydrogenation. To the best of our knowledge, KBH_4 has never been used with additives to enhance its reducing activity in transforming nitriles to amines. On the other hand, Raney nickel is routinely used as catalyst in catalytic hydrogenation ¹⁰ and heterogeneous catalytic hydride transfer hydrogenation. ¹¹ The scope of its utilization also involves the selective reduction of nitrocompounds, dinitrosubstituted diphenylsulfones, *O*- and *N*-benzyl containing nitrocompounds; the conversion of nitro olefins to carbonyl derivatives, ¹² and the synthesis of halo amines from halo nitro compounds. In these cases, the commonly used hydrogen donors are hydrazine hydrate, hydrazine derivative ¹³, ammonium formate, formic acid or cyclohexene. In 2002, Gowda *et al* ¹⁴ found that using Raney Ni / N_2H_4 / HCOOH could transform nitriles to primary amines with the yield of about 70%.

Results and Discussion

In this context, we first report a simple and convenient procedure (Scheme 1) to directly convert the robust aliphatic and aromatic nitriles **1** to the corresponding primary amines **2** with high isolated yields (over 80%) by using Raney Ni / KBH_4 system in dry ethanol at mild temperature.



R= aliphatic or aromatic substituents

Scheme 1

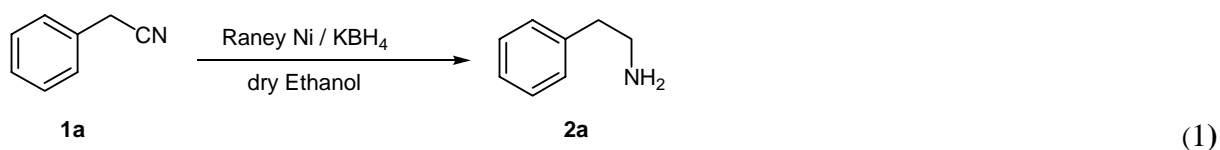


Table 1 lists the results of condition optimization experiments. To increase the yield of primary amine and at the same time to restrain the formation of second amines, excess borohydride must be used. We tried various ratio of 2-phenylacetonitrile **1a** / KBH₄, and the results showed that the more KBH₄ was used to increase the ratio from 1:4 to 1:5 (Table 1, entry 4) result no obvious increase of the yield. GC-MS experiment showed that at the ratio of 1:4, the 2-phenylethanamine was the only product, and no secondary or tertiary amine was formed. Temperature also affects the yield (Table 1, entries 5-9), when the reaction was carried out at 0 °C, the yield is higher than the reaction held at room temperature, but longer reaction time was needed. So the best condition for the reduction of aliphatic nitriles is at room temperature, and the molar ratio of substrate / Raney Ni / KBH₄ is 1:1:4.

Table 1. Optimization of the reaction conditions in the reduction of aliphatic nitrile.^a

Entry	Substrate 1a /KBH ₄ ^b	Temperature (°C)	Reaction Time (min) ^c	Yield of 2a (%) ^d
1	1:2	rt	120	43
2	1:3	rt	60	80
3	1:4	rt	45	92
4	1:5	rt	40	92
5	1:4	0	120	93
6	1:4	40	45	85
7	1:4	50	45	84
8	1:4	60	40	32
9	1:4	78	30	10

^aCommonly conditions: **1a** (10mmol), Raney Ni (moist weight 0.64g, approximately 10mmol), 25 mL dry ethanol. ^bMolar ratio. ^cMonitored by thin layer chromatography (CH₂Cl₂ : MeOH=15 : 1). ^dIsolated yield.

But, when using benzonitrile **1i** as substrate, at room temperature, the reduction needed 2 hours to complete (Table 2, entry 1), which showed that the aromatic nitriles are more difficult to be reduced than aliphatic ones. This result made us to adjust a proper temperature for the reaction using certain substrate (Table 2). 50 °C (Table 2, entry 2) is the better reaction temperature for the reduction of aromatic nitriles.

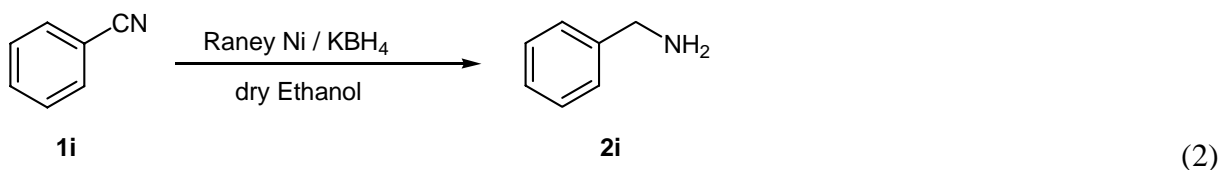


Table 2. Optimization of the reaction conditions in the reduction of benzonitrile.^a

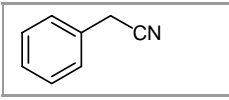
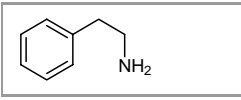
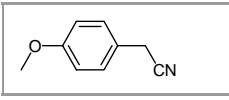
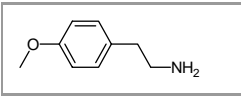
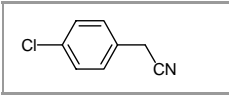
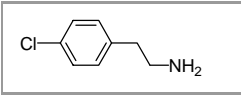
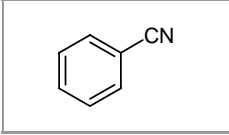
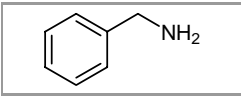
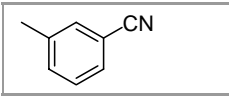
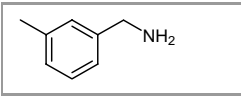
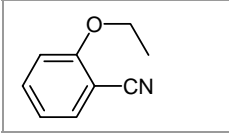
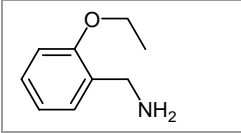
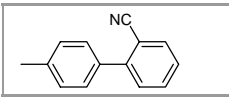
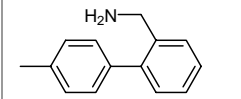
Entry	Substrate 1i /KBH ₄ ^b	Temperature (°C)	Reaction Time (min) ^c	Yield of 2i (%) ^d
1	1:4	rt	120	81
2	1:4	50	45	82
3	1:4	78	40	36

^aConditions: **1i** (10mmol), Raney Ni (moist weight 0.64g, approximately 10mmol), 25 mL dry ethanol. ^bMolar ratio. ^cMonitored by thin layer chromatography (CH₂Cl₂ : MeOH 15 : 1). ^dIsolated yield.

Changing the solvent to tetrahydrofuran (THF) or dichloromethane did dramatically harm to the reduction. The 2-phenylacetonitrile **1a** could not be reduced even in 24 hours. The reductions can work well using methanol as solvent. But due to its toxicity, we chose ethanol as the reaction solvent.

Several nitriles were chosen to be reduced under the optimized conditions, Table 3 summarizes the results. High yields were achieved for both aromatic and aliphatic nitriles. For phenylacetonitrile, the substituents, especially the electron donor substituent on phenyl ring of the substrate might lead to small decrease of the yield (Table 3, **a-c**). But for benzonitrile, the effect was not obvious (Table 3, **i-l**). For long chain aliphatic nitriles, the results were changeless, and the yields were around 82% (Table 3, **d-h**). Unfortunately, our new system has no chemoselectivity for some reducible substituents, such as nitro, aldehyde, ketone and alkene group. These were reduced together with nitrile group.

Table 3. Reduction of nitrile **1** with Raney Ni /KBH₄^a system in ethanol^b at mild temperature^c in 45 min reaction time

Entry	Nitrile 1	Temperature (°C)	Product 2	Yield(%) ^d
a		rt		92
b		rt		86
c		rt		90
d	CH ₃ (CH ₂) ₃ CN	rt	CH ₃ (CH ₂) ₄ NH ₂	80
e	CH ₃ (CH ₂) ₄ CN	rt	CH ₃ (CH ₂) ₅ NH ₂	82
f	CH ₃ (CH ₂) ₆ CN	rt	CH ₃ (CH ₂) ₇ NH ₂	81
g	CH ₃ (CH ₂) ₈ CN	rt	CH ₃ (CH ₂) ₉ NH ₂	83
h	CH ₃ (CH ₂) ₁₀ CN	rt	CH ₃ (CH ₂) ₁₁ NH ₂	82
i		50		82
j		50		80
k		50		81
l		50		86

^aMolar ratio of substrate to Raney Ni to KBH₄ = 1 : 1 : 4.^b2.5 mL of dry ethanol / mmol of substrate were used.^cRt for aliphatic nitriles and 50 °C for aromatic nitriles.^dIsolated yields.

Conclusions

In summary, a mild and efficient method for the direct hydrogenation of nitriles to primary amines has been developed. Using potassium borohydride as reducing agent, ethanol as solvent, catalyzed by readily available Raney nickel, the reaction can be carried out under mild condition without an inert atmosphere. The primary amine products are obtained in good to excellent yields, and only traces of secondary or tertiary amines are formed. Aromatic nitriles and long chain aliphatic nitriles are suitable for the reducing system.

Experimental Section

General Procedures. Mass spectra (GC/MS) were recorded on an Agilent Technologies 6890-5973N mass spectrometer. ^1H NMR spectra were recorded on a Varian Unity Inova-400 spectrometer operating in 400.00 MHz, in deuterated chloroform at room temperature. For TLC plates coated with silica gel were run in CH_2Cl_2 / MeOH mixture and spots were developed in Ultraviolet and I_2 .

Raney Nickel preparation. 10 g alloy of Ni-Al in batches were added to 50 mL NaOH aqueous solution (6 mol/L). After being stirred at 50 °C for 90 minutes, the catalyst was thoroughly washed by oxygen-free distilled water and absolute ethanol successively, and was airproofed by absolute ethanol.

General procedure for the reduction of nitrile

(The reduction of **1a**): KBH_4 2.16 g (40 mmol), Raney Ni (moist weight 0.64 g, approximately 10mmol) and 25 mL dry ethanol were placed in a 50 mL flask, and then 2-phenylacetonitrile **1a** 1.2 mL (10 mmol), was added while stirring. After vigorously stirring at room temperature for 45 min, the reaction mixture was filtered. The organic layer was evaporated and residue was dissolved in ethyl acetate, and was washed with water. The organic layer were dried and evaporated, and the product was purified by flash column chromatography on silica gel (CH_2Cl_2 / CH_3OH , 15: 1) to give 2-phenylethanamine **2a** as pale yellow liquid (yield: 92%).

2-Phenylethanamine 2a.^{15,16,17} ^1H NMR (400 MHz, CDCl_3): δ 1.26 (s, 2H, NH_2), 2.80-2.85 (m, 2H, CH_2), 3.50-3.55 (m, 2H, CH_2), 7.16–7.34 (m, 5H, Ph-H); GC-MS (ES): m/z 121 (M)⁺.

2-(4-Methoxyphenyl)ethanamine 2b.¹⁷ ^1H NMR (400 MHz, CDCl_3): δ 1.24 (s, 2H, NH_2), 2.67-2.71 (t, J 6.8 Hz, 2H, CH_2), 2.91-2.95 (t, J 6.8 Hz, 2H, CH_2), 3.79 (s, 3H, CH_3), 6.84-0.87 (m, 2H, Ph-H), 7.10-7.13 (m, 2H, Ph-H); GC-MS (ES): m/z 151 (M)⁺.

2-(4-Chlorophenyl)ethanamine 2c.¹⁸ ^1H NMR (400 MHz, CDCl_3): δ 1.23 (s, 2H, NH_2), 2.70-2.85 (m, 2H, CH_2), 2.93-2.99 (m, 2H, CH_2), 7.07-7.19 (m, 2H, Ph-H), 7.22-7.35 (m, 2H,

Ph-H); GC-MS (ES): m/z 155 (M)⁺.

Pentan-1-amine 2d.^{16,17} ¹H NMR (400 MHz, CDCl₃): δ 0.88-0.92 (m, 3H, CH₃), 1.19-1.65 (m, 8H, CH₂, NH₂), 2.70-2.96 (m, 2H, CH₂); GC-MS (ES): m/z = 87 (M)⁺.

Hexan-1-amine 2e.^{16,19} ¹H NMR (400 MHz, CDCl₃): δ 0.86-0.90 (m, 3H, CH₃), 1.26-1.57 (m, 10H, CH₂, NH₂), 2.72-2.79 (m, 2H, CH₂); GC-MS (ES): m/z 101 (M)⁺.

Octan-1-amine 2f.²⁰ ¹H NMR (400 MHz, CDCl₃): δ 0.86-0.90 (t, J 6.8 Hz, 3H, CH₃), 1.26-1.36 (m, 10H, CH₂), 1.41-1.47 (m, 2H, CH₂), 1.62-1.70 (m, 2H, NH₂), 2.67-2.70 (t, J 6.8 Hz, 2H, CH₂); GC-MS (ES): m/z 129 (M)⁺.

Decan-1-amine 2g.²⁰ ¹H NMR (400 MHz, CDCl₃): δ 0.86-0.90 (t, J 7.0 Hz, 3H, CH₃), 1.26-1.28 (m, 16H, CH₂, NH₂), 1.43-1.47 (m, 2H, CH₂), 2.67-2.71 (t, J 7.0 Hz, 2H, CH₂); GC-MS (ES): m/z 157 (M)⁺.

Dodecan-1-amine 2h.¹⁶ ¹H NMR (400 MHz, CDCl₃): δ = 0.86-0.90 (t, J 6.8 Hz, 3H, CH₃), 1.26-1.32 (m, 20H, CH₂, NH₂), 1.41-1.45 (m, 2H, CH₂), 2.66-2.69 (t, J 7.0 Hz, 2H, CH₂); GC-MS (ES): m/z 186 (M + H)⁺.

Phenylmethanamine 2i.^{15,17} ¹H NMR (400 MHz, CDCl₃): δ 1.64 (s, 2H, NH₂), 3.88 (s, 2H, CH₂), 7.23- 7.36 (m, 5H, Ph-H); GC-MS (ES): m/z 106 (M-H)⁺.

m-Tolylmethanamine 2j.¹⁵ ¹H NMR (400 MHz, CDCl₃): δ 1.64 (s, 2H, NH₂), 2.35 (s, 3H, CH₃), 3.78 (s, 2H, CH₂), 6.94-7.35 (m, 4H, Ph-H) ; GC-MS (ES): m/z 121 (M-H)⁺.

(2-Ethoxyphenyl)methanamine 2k.¹⁶ ¹H NMR (400 MHz, CDCl₃) δ 1.42-1.46 (t, J 7.2 Hz, 3H, CH₃), 1.65 (s, 2H, NH₂), 3.82 (s, 2H, CH₂), 4.04-4.09 (m, 2H, CH₂), 6.84-6.92 (m, 2H, Ph-H), 7.19-7.23 (m, 2H, Ph-H); GC-MS (ES): m/z 151(M)⁺.

(4'-Methylbiphenyl-2-yl)methanamine 2l. ¹H NMR (400 MHz, CDCl₃) δ 1.39 (s, 2H, NH₂), 2.40 (s, 3H, CH₃), 3.81 (s, 2H, CH₂), 7.21-7.36 (m, 7H, Ph-H), 7.43-7.45 (d, J 8.4 Hz, 1H, Ph-H); GC-MS (ES): m/z 196 (M - H)⁺.

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References

1. (a) Walker, E. R. H. *Chem. Soc. Rev.* **1976**, 5, 23. (b) Klenke, B.; Gilbert, I. H. *J. Org. Chem.* **2001**, 66, 2480.

2. (a) Winans, C. F.; Adkins, H. *J. Am. Chem. Soc.* **1932**, *54*, 306. (b) Juday, R.; Adkins, H. *J. Am. Chem. Soc.* **1955**, *77*, 4559. (c) Huang, Y.; Sachtler, W. M. H. *J. Catal.* **2000**, *190*, 69.
3. (a) Heinzman, S. W.; Ganem, B. *J. Am. Chem. Soc.* **1982**, *104*, 6801. (b) KuKula, P.; Studer, M.; Blaser, H. U. *Adv. Synth. Catal.* **2004**, *346*, 1487. (c) Rode, C. V.; Arai, M.; Shirai, M.; Nishiyama, Y. *Appl. Catal. A: General* **1997**, *148*, 405.
4. (a) Natsume, M.; Wada, M. *Chem. Pharm. Bull.* **1975**, *23*, 2567. (b) Kikugawa, Y.; Kruamoto, M.; Saito, I.; Yamada, S. I. *Chem. Pharm. Bull.* **1973**, *21*, 1927.
5. Nair, V.; Chun, B-K. *Arkivoc*, **2003**, (i), 9.
6. For review, see: Periasamy, M.; Thirumalaikumar, M. *J. Organometallic Chem.* **2000**, *609*, 137.
7. Khurana, J. M.; Kukreja, G. *Synth. Commun.* **2002**, *32*, 1265.
8. (a) Caddick, S.; Haynes, A. K. de K.; Judd D. B.; Williams, M. R. V. *Tetrahedron Lett.* **2000**, *41*, 3513. (b) Caddick, S.; Judd, D. B.; Lewis, A. K. de K.; Reich, M. T.; Williams, M. R. V. *Tetrahedron* **2003**, *59*, 5417.
9. (a) Liu, B.; Qiao, M. H.; Wang, J. Q.; Xie, S. H.; Li, H. X.; Fan, K. N. *J. Chem. Technol. Biotechnol.* **2003**, *78*, 512. (b) Deng, Y.; Zhou, X. S.; Nan, C. W. *Phys. Stat. Sol.* **2003**, *199*, 2265. (c) Wang, G. H.; Yu, X. B.; Cao, X. W.; Li, H. X.; Zhang, Z. R. *J. Raman Spectrosc.* **2000**, *31*, 1051. (d) Fang, J.; Chen, X. Y.; Liu, B.; Yan, S. R.; Qiao, M. H.; Li, H. X.; He, H. Y.; Fan, K. N. *J. Catal.* **2005**, *229*, 97. (e) Zhong, G. Q.; Zhou, H. L.; Zhang, J. R.; Jia, Y. Q. *Mater. Lett.* **2005**, *59*, 2252.
10. For review, see: Chen, B.; Dingerdissen, U.; Krauter, J. G. E.; Lansink H. G. J.; Möbus, K.; Ostgard, D. J.; Panster, P.; Riermeier, T. H.; Seebald, S.; Tacke, T.; Trauthwein, H. *Appl. Catal. A: General* **2005**, *280*, 17.
11. (a) Yuste, F.; Saldana, M.; Walls, F. *Tetrahedron Lett.* **1982**, *23*, 147. (b) Ayyanger, N. R.; Lugade, A. G.; Nikrad, P. V.; Sharma, V. K. *Synthesis* **1981**, 640.
12. Monti, D.; Gramatica, P.; Speranza, G.; Mannito, P. *Tetrahedron Lett.* **1983**, *24*, 147.
13. Furst, A.; Berlo, R. C.; Hooton, S. *Chem. Rev.* **1965**, *65*, 51.
14. Gowda, S.; Gowda, D. C. *Tetrahedron* **2002**, *58*, 2211.
15. Lin, R-H; Zhang, Y-M.; Zhou, Z-N. *Gaodeng Xuexiao Huaxue Xuebao*, **1990**, *11*, 889.
16. SDBSWeb : <http://riodb01.ibase.aist.go.jp/sdbs/> (National Institute of Advanced Industrial Science and Technology, date of access)
17. Guisado, C.; Waterhouse, J. E. et. al. *Org. Biomol. Chem.* **2005**, *3*, 1049.
18. Jouitteau, C.; Percec, P. Le; et. al. *Tetrahedron Lett.* **1980**, *21*, 1719.
19. Mikolasch, A.; Hammer, E.; et al. *Tetrahedron*, **2002**, *58*, 7589.
20. Kabalka, G. W.; Sastry, K. A. R.; et. al. *J. Org. Chem.* **1981**, *46*, 4296.