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A New and Convenient Method for Reduction of Oximes to Amines with $NaBH_3CN$ In the Presence of $MoCl_5/NaHSO_4{\cdot}H_2O$ System

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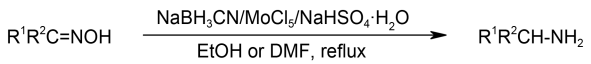
Various aldoximes and ketoximes were efficiently reduced to their corresponding amines with $NaBH_3CN$ in the presence of $MoCl_5/NaHSO_4{\cdot}H_2O$ system. Reduction reactions were carried out in refluxing EtOH or DMF within 0.3-3.8 h to afford the amines in high to excellent yields.

Key Words : Reduction, Oxime, $NaBH_3CN$, $MoCl_5$, $NaHSO_4{\cdot}H_2O$

Introduction

During the past decades, sodium borohydride has played an important role for the reduction of functional groups in modern organic synthesis.[1] This reagent is a relatively mild reducing agent and mostly used for the reduction of aldehydes and ketones in protic solvents. In order to control the reducing power of $NaBH_4$, hundreds of substituted boron hydrides have been made and introduced in chemical literature and many of them are now commercially available.[2] In fact, advances in such field have been realized by replacement of one or more hydride with other substituents, change of sodium cation to other metal, quaternary ammonium and phosphonium cations, a concurrent cation and hydride exchange, ligand metal borohydrides and finally combination of the hydride transferring agents with metals, metal salts, Lewis acids and solid supports.[3] In this context, $NaBH_3CN$ carrying an electron withdrawing cyanide group is a remarkable stable and selective reducing agent and has been found many applications in organic synthesis.[4] It is also well known that the reducing capability of $NaBH_3CN$ in reduction reactions is greatly depended to use low pH values (3-4). In spite of the great convenience of $NaBH_3CN$ in synthetic organic chemistry, however, this reagent suffers from harsh reaction conditions (strongly acidic media), limitation to use acid-sensitive functional groups and formation of some side products.

In line of the outlined strategies and our research interest to develop mild and efficient protocols for sodium cyanoborohydride reduction of functional groups in the absence of Brønsted acidic media, herein, we wish to introduce a new and convenient method for reduction of various aldoximes and ketoximes to their corresponding amines with $NaBH_3CN/MoCl_5/NaHSO_4{\cdot}H_2O$ system in refluxing EtOH or DMF (Scheme 1).



Scheme 1

Results and Discussion

Amines are important synthetic materials in organic and medicinal chemistry and they have been widely used for manufacturing of a large majority of dyes, photographic, pharmaceutical and agriculture chemicals, antioxidants and corrosion inhibitors.[5] So, the particular immense interest has been devoted to the preparation of amines by many ways.[1,2,6] In this context, reduction of oximes to amines by boron hydrides is one of the most important and easiest ways for the preparation of amines.[1,2] The literature review shows that the reduction of oximes with $NaBH_3CN$ has been rarely studied. One of the studies shows that under acidic conditions (pH 4), the reduction of ketoximes proceeds smoothly to the corresponding *N*-alkylhydroxylamine with no trace of the amine which would result from over reduction. The reduction of aldoximes is very pH-dependent. When the reduction is carried out at pH 4, the major product is the dialkylhydroxylamine, while at pH 3 the major product is the monoalkylhydroxylamine.[7] The combination system of $NaBH_3CN$ with Lewis acids such as $TiCl_3$ has been also reported for the reduction of oximes to amines.[8] However, using air sensitive titanium trichloride, harsh and acidic reaction conditions, and limitation to use the oximes which their intermediate imines can be easily hydrolyzed during the reduction are the major shortcomings of this protocol.

Recently, the combination system of $NaBH_3CN$/wet SiO_2 has been successfully reported by our research group for the efficient reduction of carbonyl compounds to the corresponding alcohols under neutral and solvent-free conditions.[9] This success encouraged us to investigate reduction of oximes with $NaBH_3CN$ in the absence of any acidic conditions.

We preliminary examined reduction of benzaldehyde oxime with $NaBH_3CN$ in refluxing EtOH under neutral conditions. The result showed that over the prolonged reaction time, the reduction did not take place and benzaldehyde oxime was completely recovered from the reaction mixture (Table 1, entry 1). Next, we turned our attention to modify the reducing capacity of $NaBH_3CN$ by the combination with

Table 1. Optimization experiments for reduction of benzaldehyde oxime with $NaBH_3CN$ under different conditions[a]

Entry	Reaction components	Molar ratio	Solvent	Time (h)	Conversion (%)
1	Oxime/$NaBH_3CN$	1:4	EtOH	3	0
2	Oxime/$NaBH_3CN$/$NaHSO_4{\cdot}H_2O$	1:4:3	EtOH	3	10
3	Oxime/$NaBH_3CN$/$MoCl_5$	1:4:1	EtOH	10	80
4	Oxime/$NaBH_3CN$/$MoCl_5$/$NaHSO_4{\cdot}H_2O$	1:4:1:1	EtOH	2	90
5	Oxime/$NaBH_3CN$/$MoCl_5$/$NaHSO_4{\cdot}H_2O$	1:4:1:3	EtOH	0.3	100
6	Oxime/$NaBH_3CN$/$MoCl_5$/$NaHSO_4{\cdot}H_2O$	1:4:1:3	MeOH	0.3	100
7	Oxime/$NaBH_3CN$/$MoCl_5$/$NaHSO_4{\cdot}H_2O$	1:4:1:3	DMF	1.5	100
8	Oxime/$NaBH_3CN$/$MoCl_5$/$NaHSO_4{\cdot}H_2O$	1:4:1:3	CH_3CN	5	50
9	Oxime/$NaBH_3CN$/$MoCl_5$/$NaHSO_4{\cdot}H_2O$	1:4:1:3	THF	5	70
10	Oxime/$NaBH_3CN$/$ZnCl_2$/$NaHSO_4{\cdot}H_2O$	1:4:1:3	EtOH	5	0
11	Oxime/$NaBH_3CN$/$CoCl_2{\cdot}6H_2O$/$NaHSO_4{\cdot}H_2O$	1:4:1:3	EtOH	5	10
12	Oxime/$NaBH_3CN$/$SnCl_2{\cdot}2H_2O$/$NaHSO_4{\cdot}H_2O$	1:4:1:3	EtOH	5	0
13	Oxime/$NaBH_3CN$/$MnCl_2{\cdot}4H_2O$/$NaHSO_4{\cdot}H_2O$	1:4:1:3	EtOH	5	0
14	Oxime/$NaBH_3CN$/$NiCl_2{\cdot}6H_2O$/$NaHSO_4{\cdot}H_2O$	1:4:1:3	EtOH	5	0
15	Oxime/$NaBH_3CN$/CuCl/$NaHSO_4{\cdot}H_2O$	1:4:1:3	EtOH	5	0
16	Oxime/$NaBH_3CN$/$CeCl_3{\cdot}7H_2O$/$NaHSO_4{\cdot}H_2O$	1:4:1:3	EtOH	5	0

[a]All reactions were carried out in 2 mL solvent under reflux conditions.

metal halides or solid inorganic weak acidic reagents such as $NaHSO_4{\cdot}H_2O$. So, performing the reduction of benzaldehyde oxime with $NaBH_3CN$ in the presence of $NaHSO_4{\cdot}H_2O$ or $MoCl_5$ showed that the efficiency of $MoCl_5$ was higher than $NaHSO_4{\cdot}H_2O$ system. However, the reactions did not complete and in contrast to the reported results,[7] benzylamine was obtained as the sole product (Table 1, entries 2 and 3).

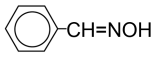
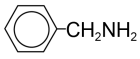
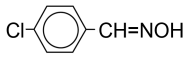
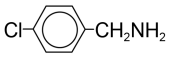
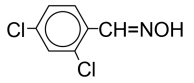
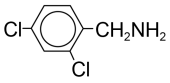
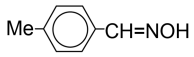
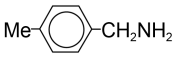
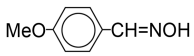
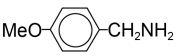
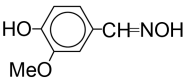
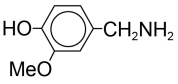
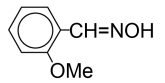
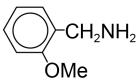
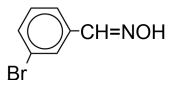
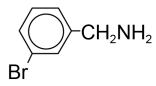
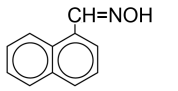
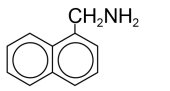
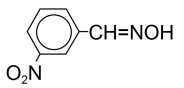
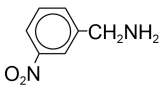
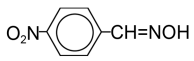
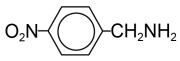
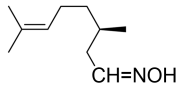
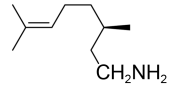
This fact and our serious demand to complete the reduction of benzaldehyde oxime with $NaBH_3CN$ prompted us to investigate the synergistic effect of $MoCl_5$ and $NaHSO_4{\cdot}H_2O$ as $NaBH_3CN$/$MoCl_5$/$NaHSO_4{\cdot}H_2O$ system on the titled reaction. An examination showed that the later system was dramatically accelerated the reduction of benzaldehyde oxime to benzylamine in refluxing EtOH. Reaction conditions were therefore optimized by performing a set of experiments using various solvents, metal halides and molar ratio of the reactants. The results of this investigation are summarized in Table 1. As seen, using the molar ratio of 4:1:3 for $NaBH_3CN$, $MoCl_5$, and $NaHSO_4{\cdot}H_2O$, respectively, in refluxing MeOH, EtOH or DMF is the optimum reaction conditions for the reduction of benzaldehyde oxime (one molar equivalent) in a perfect efficiency (Table 1, entries 5-7). We also found that the addition order of the reaction components is very important. When a solution of an oxime in ethanol or DMF was prepared, a solid mixture of $NaBH_3CN$, $MoCl_5$ and $NaHSO_4{\cdot}H_2O$ (prepared by simply mixing of the physical form of the reagents) should be added to the oxime solution. In this case the reaction afforded the amine in excellent yield. However, in other cases the reaction did not provide any satisfactory yield. In addition, an examination with Litmus paper showed that the reaction mixture had a little acidity character due to reaction components. This condition in comparison to the normally required strongly acidic conditions for $NaBH_3CN$ alone[7] or $NaBH_3CN/TiCl_3$[8] is very mild.

The utility of $NaBH_3CN$/$MoCl_5$/$NaHSO_4{\cdot}H_2O$ system was further studied by reduction of structurally different aldoximes to the corresponding primary amines at the optimized conditions (Table 2). Reduction reactions were carried out in refluxing EtOH or DMF to investigate the effect of protic and aprotic solvents on the rate enhancement. All reactions were carried out successfully under mild conditions within 0.3-3.5 h in EtOH or 1-2.8 h in DMF to afford the amines in excellent yields.

Reactivity of ketoximes to $NaBH_3CN$/$MoCl_5$/$NaHSO_4{\cdot}H_2O$ system was also examined by reduction of acetophenone oxime in refluxing EtOH or DMF. $NaBH_3CN$ in the presence of $MoCl_5$/$NaHSO_4{\cdot}H_2O$ system and with the molar ratio of 4:1:3, respectively, reduces one molar equivalent of acetophenone oxime to α-methylbenzylamine in 92-93% yield (Table 3, entry 1). The reducing capability of the examined protocol was further explored by the reduction of various ketoximes to the corresponding primary amines at the optimized conditions (Table 3). All reactions were carried out perfectly within 0.7-2.9 h to give the products in high yields. More examinations resulted that the reduction of α,β-unsaturated aldoximes and ketoximes with $NaBH_3CN$/$MoCl_5$/$NaHSO_4{\cdot}H_2O$ system was carried out regioselectively in 1,2-reduction manner. Cinnamaldehyde, benzalacetone, benzalacetophenone, 2-hydroxybenzalacetophenone and citral oximes are the oximes which were reduced successfully to the corresponding allylic amines in refluxing EtOH or DMF. The products were obtained in high to excellent yields within 0.8-3.8 h (Table 4).

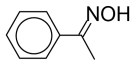
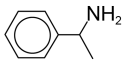
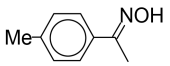
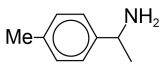
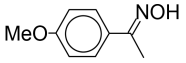
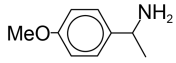
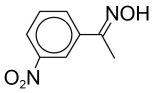
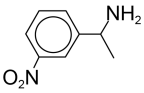
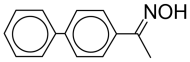
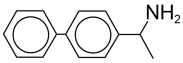
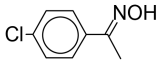
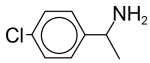
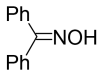
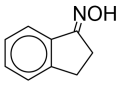
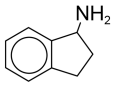
As summary, in this paper we have shown the perfect capability of $NaBH_3CN$/$MoCl_5$/$NaHSO_4{\cdot}H_2O$ system for the reduction of various aldoximes and ketoximes to the corresponding amine. The reactions were carried out in refluxing EtOH or DMF to give the products in high yields. Regioselective 1,2-reduction of α,β-unsaturated aldoximes and ketoximes was carried out successfully with this reducing system. Therefore, the enhanced reducing capacity of

Table 2. Reduction of aldoximes with $NaBH_3CN/MoCl_5/NaHSO_4{\cdot}H_2O$ system[a]

Entry	Substrate	Product	DMF		EtOH	
			Time (h)	Yield (%)[b]	Time (h)	Yield (%)[b]
1			1.5	96	0.3	95
2			2.4	94	2.2	96
3			2.8	96	2.6	98
4			1.4	94	1.2	96
5			1.3	94	1.1	95
6			1	98	0.8	98
7			1.1	95	0.9	94
8			1.2	94	0.8	95
9			2.6	97	2	97
10			2	92	3	93
11			1.7	93	3.5	93
12			1.5	98	1.2	97

[a]All reactions were carried out with the molar ratio of Subs./$NaBH_3CN$/$MoCl_5$/$NaHSO_4{\cdot}H_2O$ (1:4:1:3) under reflux conditions. [b]Yields refer to isolated pure products.

Table 3. Reduction of ketoximes with $NaBH_3CN/MoCl_5/NaHSO_4{\cdot}H_2O$ system[a]

Entry	Substrate	Product	DMF		EtOH	
			Time (h)	Yield (%)[b]	Time (h)	Yield (%)[b]
1			1.5	92	1	93
2			2.1	95	1.5	95
3			2	98	1.4	95
4			2.3	95	2	95
5			2.9	97	2.5	98
6			1.3	96	1	96
7			1.2	94	1	96
8			2.3	93	1.9	92
9			2	94	1.7	97
10			1.3	90	0.8	88
11			1.5	89	0.7	92
12			1.5	93	1.2	92

[a]All reactions were carried out with the molar ratio of Subs./$NaBH_3CN$/$MoCl_5$/$NaHSO_4{\cdot}H_2O$ (1:4:1:3) under reflux conditions. [b]Yields refer to isolated pure products.

Table 4. Reduction of conjugated oximes with $NaBH_3CN/MoCl_5/NaHSO_4{\cdot}H_2O$ system[a]

Entry	Substrate	Product	DMF		EtOH	
			Time (h)	Yield (%)[b]	Time (h)	Yield (%)[b]
1			2.5	94	2	93
2			2.9	95	2.7	93
3			3.8	98	3	98
4			3.3	96	2.8	97
5			1	89	0.8	90

[a]All reactions were carried out with the molar ratio of Subs./$NaBH_3CN$/$MoCl_5$/$NaHSO_4{\cdot}H_2O$ (1:4:1:3) under reflux conditions. [b]Yields refer to isolated pure products.

$NaBH_3CN$ in the absence of Brønsted acidic conditions, reduction of oximes to amines, the perfect regioselectivity in the preparation of allylic amines, high yield of the products are the main advantages which make this protocol a useful addition to the present methodologies.

Experimental

All reagents and solvents were purchased from commercial sources with the best quality and they were used without further purification. Oximes are prepared in high purity according to the reported procedure in literature.[10] IR and $^1H/^{13}C$ NMR spectra were recorded on Thermo Nicolet Nexus 670 FT-IR and 300 MHz Bruker spectrometers, respectively. All products are known and were characterized by their spectral data. All yields refer to isolated pure products. TLC was applied for the purity determination of substrates, products and reaction monitoring over silica gel 60 F_{254} aluminium sheet.

A Typical Procedure for Reduction of Benzaldehyde Oxime to Benzylamine with $NaBH_3CN/MoCl_5/NaHSO_4{\cdot}H_2O$ System. In a round-bottomed flask (10 mL) equipped with a magnetic stirrer and condenser, a solution of benzaldehyde oxime (1 mmol, 0.121 g) in EtOH (2 mL) was prepared. A mixture of $NaBH_3CN$ (4 mmol, 0.251 g), $MoCl_5$ (1 mmol, 0.273 g) and $NaHSO_4{\cdot}H_2O$ (3 mmol, 0.414 g) in solid state was prepared and then added to the oxime solution. The resulting mixture was continued to stirring under reflux condition for 20 min. TLC monitored the progress of the reaction. After completion of the reaction, aqueous $NaHCO_3$ (5%, 10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The extracts were combined and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure and thereafter short column chromatography of the resulting crude product over silica gel afforded the pure liquid benzylamine (0.102 g, 95% yield) (Table 2).

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References

1. (a) Hudlicky, M. *Reductions in Organic Chemistry*; Ellis Horwood: Chichester, 1984. (b) Abdel-Magid, A. F. *Reductions in Organic Synthesis*; ACS Symposium Series, 1996; Vol. 641. (c) Burke, S. D.; Danheiser, R. L. *Handbook of Reagents for Organic Synthesis, Oxidizing and Reducing Agents*; Wiley-VCH: New York, 1999. (d) Andersson, P. G.; Munslow, I. J. *Modern Reduction Methods*; Wiley-VCH: New York, 2008.
2. Seyden-Penne, J. *Reductions by the Alumino and Borohydrides in Organic Synthesis*, 2nd ed.; Wiley-VCH: New York, 1997.
3. (a) Review: Firouzabadi, H.; Zeynizadeh. B. *Iranian J. Sci. Tech. Trans. A* **1995**, *19*, 103. (b) Firouzabadi, H.; Zeynizadeh, B. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 155. (c) Firouzabadi, H.; Adibi, M.; Zeynizadeh, B. *Synth. Commun.* **1998**, *28*, 1257. (d) Zeynizadeh, B. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 317. (e) Zeynizadeh, B.; Shirini, F. *Bull. Korean Chem. Soc.* **2003**, *24*, 295. (f) Zeynizadeh, B.; Faraji, F. *Bull. Korean Chem. Soc.* **2003**, *24*, 453. (g) Zeynizadeh, B.; Yahyaei, S. *Bull. Korean Chem. Soc.* **2003**, *24*, 1664. (h) Zeynizadeh, B.; Shirini, F. *J. Chem. Res.* **2003**, 335. (i) Zeynizadeh, B.; Zahmatkesh, K. *J. Chem. Res.* **2003**, 522. (j) Zeynizadeh, B.; Zahmatkesh, K. *J. Chin. Chem. Soc.* **2003**, *50*, 267. (k) Zeynizadeh, B. *Z. Naturforsch.* **2003**, *58b*, 1220. (l) Zeynizadeh, B.; Yahyaei, S. *Z. Naturforsch.* **2004**, *59b*, 699. (m) Zeynizadeh, B.; Yahyaei, S. *Z. Naturforsch.* **2004**, *59b*, 704. (n) Zeynizadeh, B.; Behyar, T. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 307. (o) Zeynizadeh, B.; Behyar, T. *J. Braz. Chem. Soc.* **2005**, *16*, 1200. (p) Zeynizadeh, B.; Zahmatkesh, K. *J. Chin. Chem. Soc.* **2005**, *52*, 109. (q) Zeynizadeh, B. *J. Chin. Chem. Soc.* **2005**, *52*, 525. (r) Zeynizadeh, B.; Setamdideh, D. *J. Chin. Chem. Soc.* **2005**, *52*, 1179. (s) Zeynizadeh, B.; Behyar, T. *Z. Naturforsch.* **2005**, *60b*, 453. (t) Zeynizadeh, B.; Ghasemi, H. *J. Chem. Res.* **2006**, 542. (u) Zeynizadeh, B.; Setamdideh, D. *Synth. Commun.* **2006**, *36*, 2699. (v) Setamdideh, D.; Zeynizadeh, B. *Z. Naturforsch.* **2006**, *61b*, 1275. (w) Zeynizadeh, B.; Setamdideh, D., Faraji, F. *Bull. Korean Chem. Soc.* **2008**, *29*, 76. (x) Zeynizadeh, B.; Setamdideh, D. *Asian J. Chem.* **2009**, *21*, 3603.
4. (a) Hutchins, R. O.; Maryanoff, B. E.; Milewski, C. A. *J. Am. Chem. Soc.* **1971**, *93*, 1793. (b) Hutchins, R. O.; Milewski, C. A.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1973**, *95*, 3662. (c) Hutchins, R. O.; Kacher, M.; Rua, L. *J. Org. Chem.* **1975**, *40*, 923. (d) Lane, C. F. *Synthesis* **1975**, 135. (e) Hutchins, R. O.; Rotstein, D.; Natale, N.; Fanelli, J. *J. Org. Chem.* **1976**, *41*, 3328. (f) Hutchins, R. O.; Kandasamy, D.; Maryanoff, C. A.; Masilamani, D.; Maryanoff, B. E. *J. Org. Chem.* **1977**, *42*, 82. (g) Hutchins, R. O.; Taffer, I. M.; Burgoyne, W. *J. Org. Chem.* **1981**, *46*, 5214. (h) Kim, S.; Oh, C. H.; KO, J. S.; Ahn, K. H.; Kim, Y. J. *J. Org. Chem.* **1985**, *50*, 1927. (i) Han, O.; Shih, Y.; Liu, L.-D.; Liu, H.-W. *J. Org. Chem.* **1988**, *53*, 2105. (j) Paquette, L. A.; Crich, D.; Fuchs, P. L.; Molander, G. A. *Encyclopedia of Reagents for Organic Synthesis*, 2nd ed.; Wiley-VCH: Weinheim, 2009.
5. (a) Ricci, A. *Modern Amination Methods*; Wiley-VCH: Weinheim, 2000. (b) Lawrence, S. A. *Amines: Synthesis, Properties and Applications*; Cambridge University Press: U.K. 2004. (c) Nugent, T. C. *Chiral Amine Synthesis: Methods, Developments and Applications*; Wiley-VCH: Weinheim, 2010. (d) Farooqui; T.; Farooqui, A. A. *Biogenic Amines: Pharmacological, Neurochemical and Molecular Aspects in the CNS*; Nova Science Publisher: New York, 2010.
6. (a) Hagen, J. *Industrial Catalysis: a Practical Approach*, 2nd ed.; Wiley-VCH: Weinheim, 2006. (b) Arpe, H. -J. *Industrial Organic Chemistry*, 5th ed.; Wiley-VCH: Weinheim, 2010.
7. Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.
8. Leeds, J. P.; Kirst, H. A. *Synth. Commun.* **1988**, *18*, 777.
9. Kouhkan, M.; Zeynizadeh, B. *Bull. Korean Chem. Soc.* **2010**, *31*, 2961.
10. Zeynizadeh, B.; Amjadi, E. *Asian J. Chem.* **2009**, *21*, 3611 and the references cited therein.