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One-Pot Reductive Amination of Carbonyl Compounds Using Sodium Borohydride-Cellulose Sulfuric Acid

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A fast, efficient, and high yielding method for the preparation of amines by reductive amination of aldehydes and ketones using sodium borohydride in the presence of cellulose sulfuric acid in EtOH and under solvent-free conditions at room temperature is described.

Key Words: Cellulose sulfuric acid, Reductive amination, Carbonyl compounds, Amines, $NaBH_4$

Introduction

Direct reductive amination of aldehydes and ketones is a convenient method for the preparation of secondary and tertiary amines owing to its simple procedure[1] and recent application of the reaction to combinatorial chemistry is gaining more attention.[2] A variety of reducing agents, such as hydrogen in the presence of metal catalysts,[3] $NaBH_3CN$,[4] $NaBH(OAC)_3$,[5] silica gel-$Zn(BH_4)_2$,[6] Ti(O-*i*-Pr)$_4$-$NaBH_4$,[7] $NaBH_4$-H_2SO_4,[8] $NaBH_4$-$ZrCl_4$,[9] $NaBH_4$-$NiCl_2$,[10] $NaBH_4$-wet-clay-microwave,[11] pyridine-BH_3,[12] $NaBH_4$-H_3BO_3,[13] $Zr[(BH_4)_2(Cl)_2(dabco)_2]$,[14] Et_3-SiH-CF_3CO_2H,[15] $NaBH_4$ in micellar media,[16] zinc borohydride *N*-methyl piperidine,[17] $NaBH_4$-$H_3PW_{12}O_{40}$,[18] $NaBH_4$-Silica phosphoric acid,[19] zinc borohydride *N*-methyl pyrrolidine[20] $NaBH_4$-Silica-Gel-supported sulfuric acid,[21] $NaBH_4$-Amberlyst 15[22] and $NaBH_4$-silica chloride[23] have been developed.

However, most of these methods suffer from one or more drawbacks. For example, hydrogenation is not compatible with compounds that contain a carbon-carbon double or triple bond and several other reducible functional groups such as nitro, cyano and furyl groups.[24]

Usually pyridine-BH_3 from commercial sources was utilized without further purification, because this reagent is quite unstable to heat and attempted distillation of the liquid residue at reduced pressures sometimes resulted in violent decompositions. Thus, extreme care must be used if this reagent is handled in large quantities.[25] $NaBH(OAC)_3$ is flammable, water-reactive, and poorly soluble in most of the commonly used organic solvents. Cyanoborohydride and tin hydrid reagents are highly toxic and generate toxic by-products such as HCN, NaCN or organotin compounds upon workup and may result in the contamination of the product with the toxic compounds.[26] Furthermore, they are not environmentally friendly and are not accepted in the concept of green chemistry.

Sodium borohydrid is an inexpensive, safe to handle and environmental friendly reducing agent which rapidly reduces aldehydes, ketones and acid chlorides.

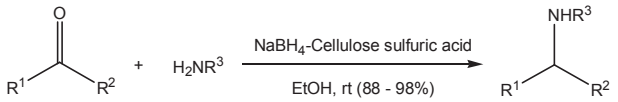
Cellulose sulfuric acid is very active, stable to air and moisture, nontoxic and inexpensive. Cellulose sulfuric acid is prepared *via* reaction between cellulose and chlorosulfunic acid.[27] In addition, it can be quantitatively recovered by filtration and reused.

Now we report that an efficient and smooth reductive amination of a variety of carbonyl compounds proceed using $NaBH_4$ in the presence of cellulose sulfuric acid both in EtOH as a solvent (Scheme 1) and under solvent-free conditions (Scheme 2).

Experimental

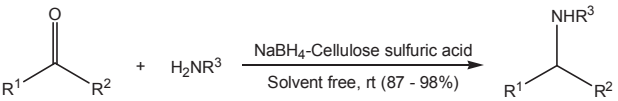
Preparation of cellulose sulfuric acid.[27] To a magnetically stirred mixture of cellulose (5.00 g, DEAE for column chromatography, Merck) in $CHCl_3$ (20 mL), chlorosulfonic acid (1.00 g, 9 mmol) was added dropwise at 0 °C during 2 h. After completion of the addition, the mixture was stirred for 2 h until HCl was removed from reaction vessel. Then, the mixture was filtered and washed with methanol (30 mL) and dried at room temperature to obtain cellulose sulfuric acid as white powder (5.22 g). The number of H^+ site of cellulose-SO_3H (0.50 meq/g) determined by acid-base titration. This value corresponds to about 90% of the sulfur content, indicating that most of the sulfur species on the sample are in the form of the sulfonic acid groups.

General procedure for the reductive amination of carbonyl compounds in EtOH (Method I). Carbonyl compound (1 mmol) and amine (1 mmol) were mixed in EtOH (3 mL) and then was added cellulose sulfuric acid (0.1 g). The mixture vigorously



R^1 = H, alkyl, aryl R^2, R^3 = alkyl, aryl

Scheme 1. Reductive amination of carbonyl compounds by $NaBH_4$ in the presence of cellulose sulfuric acid in EtOH



R^1 = H, alkyl, aryl R^2, R^3 = alkyl, aryl

Scheme 2. Reductive amination of carbonyl compounds by $NaBH_4$ in the presence of cellulose sulfuric acid under solvent-free conditions

Table 1. Reductive amination of aldehydes and ketones using $NaBH_4$-cellulose sulfuric acid[a]

Entry	Carbonyl Compound	Amine	Method I[b]		Method II[c]		Ref.
			Time (min)	Yield[d] (%)	Time (min)	Yield[d] (%)	
1	PhCHO	$PhNH_2$	45	94	4	96	[25]
2	4-Cl-PhCHO	$PhNH_2$	20	91	11	92	[11]
3	2-NO_2-PhCHO	$PhNH_2$	44	94	24	88	[11]
4	4-CN-PhCHO	$PhNH_2$	125	92	34	97	[26]
5	2-Cl-PhCHO	$PhNH_2$	57	89	35	87	[27]
6	4-OMe-PhCHO	$PhNH_2$	7	95	6	97	[11]
7	4-CH_3-PhCHO	$PhNH_2$	45	91	22	93	[28]
8	PhCHO	4-Cl-$PhNH_2$	95	89	8	95	[26]
9	PhCHO	4-OEt-$PhNH_2$	4	88	3	89	[14]
10	PhCHO	4-CH_3-$PhNH_2$	12	95	3	98	[29]
11	PhCHO	4-OMe-$PhNH_2$	22	88	7	87	[11]
12	PhCHO	4-NO_2-$PhNH_2$	170	90	5	92	[30]
13	PhCHO	Morpholine	7	93	2	92	[25]
14	PhCHO	$PhCH_2NH_2$	2	94	2	95	[13]
15	PhCHO	Piperidine	6	97	1	95	[25]
16	PhCHO	Pyrrolidine	6	98	1	97	[31]
17	Cyclohexanone	$PhNH_2$	28	91	4	94	[35]
18	Cyclohexanone	Piperidine	5	90	1	92	[25]
19	Cyclohexanone	Pyrrolidine	5	95	1	95	[31]
20	Cyclohexanone	$PhCH_2NH_2$	2	96	1	94	[25]
21	2-Heptanone	$PhNH_2$	4	94	2	96	[32]
22	Cinamaldehyde	$PhNH_2$	4	97	2	90	[28]
23	Butanal	$PhNH_2$	18	89	5	91	[30]
24	PhCHO	$EtNH_2$	2	93	1	94	[18]
25	PhCHO	PhNH-Me	8	95	2	97	[33]

[a]All reactions were carried out at room temperature and molar ratio of reagent/amine/carbonyl compound was 1/1/1 and 0.1 g cellulose sulfuric acid was used. [b]Method I: Reaction was carried out in EtOH. [c]Method II : reaction was carried out under solvent-free condition. [d]Yield refer to pure isolated product.

stirred at room temperature and $NaBH_4$ (1 mmol) was added and the mixture was stirred. After completion of the reaction as indicated by TLC, the mixture was filtered and the residue was washed with CH_2Cl_2 (2 × 15 mL). The solvent was evaporated and the crude product was purified by column chromatography on silica gel (eluent: *n*-hexane/EtOAc: 18/2).

General procedure for the reductivea of carbonyl compounds under solvent-free conditions (Method II). Carbonyl compound (1 mmol) and amine (1 mmol) was ground with $NaBH_4$ (1 mmol) in the presence of cellulose sulfuric acid (0.1 g) under solvent-free conditions at room temperature. After completion of the reaction as monitored by TLC, the mixture was washed with CH_2Cl_2 (2 × 25 mL) and the combined solvent was dried over $MgSO_4$.

Evaporation of the solvent and a short-column chromatography of the product on silica gel (eluent: *n*-hexane/EtOAc: 18/2) gave the pure product. After work-up all products were characterized spectroscopically (^{1}H NMR and IR) and showed physical and spectral data in accordance with their expected structure by comparison with authentic samples.

Results and Discussion

Initially, the condensation of benzaldehyde with aniline was chosen as the model reaction, to examine the effect of the $NaBH_4$-cellulose sulfuric acid in EtOH as the solvent (method I) and under solvent-free conditions (method II). In both methods the reaction was carried out with an equimolar ratio of benzaldehyde, aniline and sodium borohydride and the pH of the mixture was adjusted to neutrality by addition of cellulose sulfuric acid at room temperature. In method I after 45 min, TLC showed complete disappearance of imine and in method II, the reaction took place within 4 min. After work-up of the reaction mixture in both methods, *N*-benzylaniline was obtained in excellent isolated yield (94 and 96% respectively).

We then applied these optimal conditions for the reductive amination of various aldehydes and ketones with aliphatic and aromatic amines and these transformations were successful and gave the desired products in good to excellent yields (87 - 98%) as shown in Table 1.

As indicated in Table 1, when treated with aniline in the presence of $NaBH_4$-cellulose sulfuric acid, benzaldehyde functionalized with reducible functional groups such as C=C, CN and NO_2 afforded the corresponding amines without reduction of the carbon-carbon double bond, CN and NO_2 groups (Table 1, entries 3, 4, 22). Similarly, aliphatic and cyclic ketones underwent reductive amination successfully to give the corresponding amines in excellent yields (Table 1, entries 17-21). This method can be used for anilines with electron-withdrawing groups which is not possible with [$NaBH_3CN$] and [$NaBH(OAC)_3$],

Table 2. Comparison of cellulose sulfuric acid and the other reducing agents in reductive amination of aldehyde and ketones

Entry	Carbonyl Compound	Amine	$NaBH_4$-Cellulose sulfuric acid				Other reducing agent					
			Method I[a]		Method II[b]							
			Time (min)	Yield[d] (%)	Time (min)	Yield[d] (%)	Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)
1	PhCHO	$PhNH_2$	45	94	4	96	90	94[c]	120	92[d]	-	-
2	PhCHO	$PhCH_2NH_2$	2	94	2	95	20	93[e]	90	93[d]	-	-
3	PhCHO	Morpholine	7	93	2	92	60	83[f]	10	94[g]	30	0[h]
4	Cyclohexanone	Piperidine	5	90	1	92	-	-	60	97[d]	-	-
5	Cyclohexanone	$PhNH_2$	28	91	4	94	45	85[e]	2	95[g]	240	91

[a]Method I: Reaction was carried out in EtOH. [b]Method II: Reaction was carried out under solvent-free conditions. [c]$Cu(pph_3)_2BH_4$·MeOH.[34] [d]ZBHNMP (zinc borohydride *N*-methyl pyrrolidine).[20] [e]2-(Tributylamino)-ethoxyborohydride.[36] [f]Zinc-modified cyanotrihydroborate[28] [g]$NaBH_4$-silica phosphoric acid.[19] [h]$NaBH_4$-H_3BO_3.[13]

the most often used reagents for this purpose (Table 1, entry 8 and 12). However, in order to examine a wider range of amines and to better illustrate the scope and limitation of this method, we investigated the reaction with both primary and secondary amines such as benzylamine, piperidine, pyrrolidine and morpholine using PhCHO as a representative aldehyde, and cyclohexanone as a representative ketone (Table 1, entries 13-16, 18-20). Reductive amination of aliphatic aldehyde, such as butanal with aniline also gives excellent yield of corresponding amine (Table 1, entry 23).

Under this condition carbonyl compounds were not reduced in the reaction mixture, whereas the imine intermediates were converted easily to the corresponding amines. However, the absence of formation of any hydroxyl compound in these reductions suggests that the overall process would proceed successfully if a reasonable concentration of imines is available and the reaction conditions could discriminate between the reduction of the imine intermediate and the carbonyl compound present in the reaction mixture.

In order to show the advantages and drawbacks of our method, we have compared some of our results with those reported in the literature in Table 2. As indicated in Table 2, in many cases our results were superior to others. For example, we compared the reductive amination of cyclohexanone with aniline using $Cu(PPh_3)_2BH_4$ *vs.* $NaBH_4$-cellulose sulfuric acid (Table 2, entry 5). The reaction with $Cu(PPh_3)_2BH_4$ in methanol was completed in 4 h, while this reaction with $NaBH_4$-cellulose sulfuric acid either in ethanol or under solvent-free took 28 or 4 minutes.

In another comparison, the reductive amination of benzaldehyde with morpholine using $NaBH_4$-H_3BO_3 under solvent-free conditions, benzyl alcohol was obtained in 99% yield after 30 min as a major product, while in our method using $NaBH_4$-cellulose sulfuric acid, corresponding alcohol was not obtained, and reaction was completed in 2 min with the high yield of *N*-benzylmorpholine (Table 2, entry 3).

Conclusion

In conclusion, present procedure using an efficient and environmentally friendly bio-supported proton source and $NaBH_4$ for the reductive amination of aldehydes or ketones provides a novel protocol for synthesis of amines. Moreover, easy reaction work-up, high reaction rates and yields and neutral condition make this method more useful for this purpose.

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References

1. Hutchins, R. O.; Hutchins, M. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 8, p 25.
2. Gustafsson, M.; Olsson, R.; Anderson, C. M. *Tetrahedron Lett.* **2001**, *42*, 133.
3. a) Tarasevich, V. A.; Kozlov, N. G. *Russ. Chem. Rev.* **1999**, *68*, 55. b) Nugent, T. C.; Ghosh, A. K.; Wakchaure, V. N.; Mohanty, R. R. Adv. *Synth. Catal.* **2006**, *348*, 1289.
4. Lane, C. F. *Synthesis* **1975**, 135.
5. Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849.
6. Ranu, B. C.; Majee, A.; Sarkar, A. *J. Org. Chem.* **1998**, *63*, 370.
7. a) Neidigh, K. A.; Avery, M. A.; Williamson, J. C.; Bhattacharyya, S. *J. Chem. Soc. Perkin Trans. 1* **1998**, 2527. b) Bhattacharyya, S.; Chatterjee, A.; Williamson, J. S. *Synlett* **1995**, *10*, 1079.
8. Verardo, G.; Giumanin, A. G.; Strazzolini, P.; Poiana, M. *Synthesis* **1993**, 121.
9. Bhattacharyya, S. *J. Org. Chem.* **1995**, *60*, 4928.
10. Saxena, I.; Borah, R.; Sarma, J. C. *J. Chem. Soc. Perkin Trans. 1* **2000**, 503.
11. Varma, R. S.; Dahiya, R. *Tetrahedron* **1998**, *54*, 6293.
12. Bomann, M. D.; Guch, I. C.; Dimare, M. *J. Org. Chem.* **1995**, *60*, 5995.
13. Cho, B. T.; Kang, S. K. *Tetrahedron* **2005**, *61*, 5725.
14. Firouzabadi, H.; Iranpoor, N.; Alinezhad, H. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 143.
15. Chen, B. C.; Sundeen, J. E.; Guo, P.; Bednarz, M. S.; Zhao, R. *Tetrahedron Lett.* **2001**, *42*, 1245.
16. Alinezhad, H.; Tajbakhsh, M.; Salehian, F. *Monatsh. Chem.* **2005**, *136*, 2029.
17. Alinezhad, H.; Tajbakhsh, M.; Zamani, R. *Synlett* **2006**, 431.
18. Alinezhad, H.; Ardestani, E. *Lett. Org. Chem.* **2007**, *4*, 473.
19. Alinezhad, H.; Tajbakhsh, M.; Enayati Ahangar, R. *Monatsh. Chem.* **2008**, *13*, 21.
20. Alinezhad, H.; Tajbakhsh, M.; Salehian, F.; Fazli, K. *Tetrahedron Lett.* **2009**, *50*, 659.
21. Alinezhad, H.; Tajbakhsh, M.; Zare, M. *Syn. Commun.* **2009**, *39*, 2907.

22. Alinezhad, H.; Tajbakhsh, M.; Mahdavi, N. *Syn. Commun.* **2010**, *40*, 951.
23. a) Alinezhad, H.; Tajbakhsh, M.; Hamidi, N. *Turk. J. Chem.* **2010**, *34*, 1. b) Alinezhad, H.; Tajbakhsh, M.; Hamidi, N. *Chin. Chem. Lett.* **2010**, *21*, 7.
24. Rylabder, P. N. *Hydrogenation Methods*; Academic Press: New York, 1985.
25. a) Ryschkewitsch, G. E.; Birnbaum, E. R. *Inorg. Chem.* **1965**, *4*, 575. b) Baldwin, R. A.; Washburn, R. M. *J. Org. Chem.* **1961**, *26*, 3549.
26. a) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897. b) Pereyre, M.; Quintard, J. P.; Rahm, A. *Tin in Organic Synthesis*; Butterworths: London, 1987; p 6.
27. Shaabani, A.; Maleki, A. *Appl. Catal. A* **2007**, *331*, 149.
28. Kim, S.; Oh, C. H.; Ko, J. S.; Ahn, K. H.; Kim, Y. *J. Org. Chem.* **1985**, *50*, 1927.
29. a) Onaka, M.; Umezono, A.; Kawai, M.; Izumi, Y. *J. Chem. Soc. Chem. Commun.* **1985**, *17*, 1202. b) Watanabe, Y.; Tsuji, Y.; Ige, H.; Ohsugi, Y.; Ohta, T. *J. Org. Chem.* **1984**, *49*, 3359.
30. Kessar, S. V.; Gopal, R.; Singh, M. *Tetrahedron* **1973**, *29*, 167.
31. Cho, B. T.; Kang, S. K. *Synlett* **2004**, 1484.
32. Vijayaraj, M.; Gopinath, C. H. *Appl. Catal.* **2007**, *320*, 807.
33. Abdel-Magid, A. F.; Maryanoff, C. F. *Synlett* **1990**, 537.
34. Bhanushali, M. J.; Nandurkar, N. S.; Bhor, M. D.; Bhanage B. M. *Tetrahedron Lett.* **2007**, *48*, 1273.
35. Abdel-Magid, A. F.; Maryanoff, C. F.; Carson, K. C. *Tetrahedron Lett.* **1990**, *31*, 5595.
36. Mohanazadeh, F.; Forozani, M.; Taheri, A. *Monatsh. Chem.* **2007**, *138*, 1187.