REGULAR ARTICLE

One-pot Reductive Amination of Carbonyl Compounds with $\text{NaBH}_4\text{-B}(\text{OSO}_3\text{H})_3/\text{SiO}_2$ in Acetonitrile and in Solvent-free Condition

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Abstract. An efficient one-pot procedure for the direct reductive amination of aldehyde and ketones was achieved in the presence of sodium borohydride by using $\text{B}(\text{OSO}_3\text{H})_3/\text{SiO}_2$ (SBSA) as the reusable solid catalyst in acetonitrile and solvent-free conditions. Both aromatic and aliphatic aldehyde reacted well to give the corresponding amines in excellent yields. All the products are known and well-characterized. The catalyst is recoverable and could be easily recycled by filtration and reused several times without any significant loss of its activity. SBSA acts as a dual Brønsted/Lewis acid that is an air-stable and cost-effective solid acid.

Keywords. Reductive amination; boron trisulfonic acid; catalysis; NaBH_4 .

1. Introduction

One of the important method for the synthesis of primary, secondary and tertiary amines is the reductive amination of aldehydes and ketones.¹ Reductive amination is a great and trustworthy approach for the formation of C–N bonds, which can avoid the problem of over-alkylation that often accompanies direct alkylation of amines with alkyl halides.^{2–4} In this reaction, an amine and a carbonyl compound condense to afford an imine or iminium ion in one- or two-step procedure that is reduced *in situ* or subsequently to form an amine product. Another problem during reductive amination of carbonyl compounds with primary amines is over-alkylation and direct reduction of carbonyl compound to the corresponding alcohol. In these cases, formation and isolation of the imines which followed by reduction can avoid the problem, but the need to isolate imines make its synthetic utility poor.⁵

A large number of reducing hydride reagents have been studied for direct reductive amination avoiding the direct reduction of starting carbonyl compound to the corresponding alcohol, including sodium cyanoborohydride (NaBH_3CN),⁶ Pyridine- BH_3 ,⁷ sodium triacetoxyborohydride ($\text{NaBH}(\text{OAc})_3$),⁸ hydrosiloxane reagent,⁹ titanium(IV) isopropoxide,¹⁰ and Zirconium (IV) isopropoxide.¹¹ However, many of these methods suffer from diverse disadvantages such as toxic compounds as by-product, hygroscopicity and thermal instability of the reagents, incompatibility with compounds containing

a carbon–carbon double or triple bond and other reducible functional groups such as cyano and nitro groups. One of the best reagents for reductive amination is NaBH_3CN , which chemoselectively reduces iminium ions over aldehydes or ketones. However, this reagent can liberate hydrogen cyanide when the reaction is quenched, which is highly toxic.⁶ Another chemoselective reducing agent that has been used is sodium triacetoxyborohydride ($\text{NaBH}(\text{OAc})_3$), but it is unstable in hydroxylic solvents such as methanol and water.⁹

Sodium borohydride (NaBH_4) is a safe, green, environment-friendly and inexpensive reducing agent, so it has been the conclusive choice for the direct reductive amination process and has been used with various catalysts.¹² However, its application is restricted, in view of the fact that it is accomplished to reduce other reducible functional groups in the molecule.

NaBH_4 is able to reduce imines as well as carbonyls (aldehydes and ketones) in the same way. To prevent the reduction of carbonyl group in the one-pot process, the carbonyl-amine condensation reaction must be completed before addition of Sodium borohydride. NaBH_4 has been used in combination with various catalysts, which assist imine formation, for successful reductive amination, such as: Cellulose sulfuric acid,¹³ $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$,¹⁴ $\text{SiO}_2\text{-Zn}(\text{BH}_4)_2$,¹⁵ $\text{Ti}(\text{OR})_4$,¹⁶ wet-clay-microwave,¹⁷ H_2SO_4 ,¹⁸ ZrCl_4 ,¹⁹ NiCl_2 ,²⁰ H_3BO_3 ,²¹ silica chloride,²² micellar media,²³ $\text{H}_3\text{PW}_{12}\text{O}_{40}$,²⁴ Silica phosphoric acid,²⁵ Silica-Gel-supported sulfuric acid,²⁶ Amberlyst 15,²⁷ DOWEX(R)50WX8,²⁸ $\text{B}(\text{C}_6\text{F}_5)_3$,²⁹ microwave mediated,³⁰ and Ni-complex supported Fe_3O_4 .³¹

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Scheme 1. Preparation of $\text{B}(\text{OSO}_3\text{H})_3/\text{SiO}_2$.

Scheme 2. Reductive amination of carbonyl compounds by NaBH_4 catalyzed by SBSA in CH_3CN and under solvent-free conditions.

$\text{B}(\text{OSO}_3\text{H})_3/\text{SiO}_2$ (SBSA)^{32,33} is a trifunctional inorganocatalyst that works as a strong acid (soluble in water and polar solvent) which was simply prepared by addition of chlorosulfonic acid to boric acid under N_2 atmosphere at room temperature and then mixed with SiO_2 by 1:5 ratio (Scheme 1) and characterized by FT-IR spectroscopy. According to the FT-IR spectra, the bands at $\sim 1160\text{ cm}^{-1}$ are related to symmetric stretching vibration of $\text{O}=\text{S}=\text{O}$, and the band centered at 650 cm^{-1} is related to stretching vibration of $\text{S}-\text{O}$. The band at 1105 cm^{-1} is attributed to $\text{O}-\text{Si}$ vibration. The broad and intense $\text{O}-\text{H}$ stretching absorption band appears in the region of 3350 cm^{-1} . Due to the current challenges for developing green and environmentally benign chemical processes, and using solid reusable catalyst, we report herein the details of direct reductive amination of aldehydes and ketones using sodium borohydride- $\text{B}(\text{OSO}_3\text{H})_3/\text{SiO}_2$ for the first time (Scheme 2).

2. Experimental

2.1 General remarks

Chemicals were purchased from Merck and Fluka and used as received. FT-IR spectra were obtained using BOMEM MB-Series 1998 FT-IR spectrometer. ^1H NMR spectra were run on Bruker Avance spectrometer (DRX 500 MHz). The progress of the reaction was followed with TLC, using silica gel SILG/UV 254 plates. All the products are known and were characterized by comparison of their spectra (IR, ^1H NMR) and TLC with those reported in the literature.

2.2 General procedure

To a mixture of aldehyde (1 mmol), amine (1.2 mmol) and SBSA (0.05 g) in CH_3CN (5 mL) or under solvent-free

condition was added NaBH_4 (2 mmol, 72 mg), and then the reaction mixture was stirred at room temperature (25°C) with a magnetic stirrer for 10–20 min. After completion, EtOAc (10 mL) was added to the reaction mixture, and the catalyst was easily filtered; then, crude product was washed with H_2O (2–10 mL) and a saturated solution of NaHCO_3 and dried over anhydrous Na_2SO_4 . After removal of the solvent, the pure product was obtained and further purified by recrystallization with a suitable solvent (ether or CHCl_3).

2.3 Spectral data

The structure of the products was confirmed by FT-IR, ^1H , ^{13}C NMR, and compared with the corresponding reported spectral data.^{21–29} Spectroscopic data for a selected compound is presented below:

2.3a *N*-(4-Nitro Benzyl) Aniline (Table 3, Entry 6): ^1H NMR (500 MHz, CDCl_3): δ 4.51 (s, CH_2), 6.63 (d, 2H, $J=9.5\text{ Hz}$), 6.80 (t, 1H, $J=9\text{ Hz}$), 7.22 (t, 2H, $J=12\text{ Hz}$), 7.56 (d, 2H, $J=11\text{ Hz}$), 8.22 (d, 2H, 12 Hz); ^{13}C NMR (140 MHz, CDCl_3) δ 47.8 (CH_2), 113.2 (CH Ar), 118.5 (CH Ar), 123.9 (CH Ar), 127.8 (CH Ar), 129.4 (CH Ar), 146.9 (CH Ar), 147.2 (CH Ar).

3. Results and Discussion

We started with optimization of the reaction conditions by the model reaction of benzaldehyde/aniline at room temperature. The effects of the reaction conditions, such as amount of catalyst, reaction time and different solvents on the catalytic performance of SBSA were examined. Table 1 summarizes the results obtained for different amount of catalyst which shows that the best performance is seen in the presence of 0.05 g amount of SBSA. The results presented in Table 2 point out that the reaction of benzaldehyde and aniline exhibited

Table 1. Optimization of the amount of catalyst.

Entry	Catalyst (g)	Time (min)	Yield (%)
1	0.15	10	50
2	0.1	10	68
3	0.05	5	85
4	0.02	15	80

Table 2. Solvent selection.

Entry	Solvent	Time (min)	Yield (%)
1	H ₂ O	180	80
2	EtOH	90	70
3	CH ₃ CN	10	95
4	PEG-300	50	80
5	THF	120	60
6	CHCl ₃	180	20
7	Solvent-free	5	96

Reaction conditions: 1 mmol benzaldehyde, 1.2 mmol aniline and 2 mmol NaBH₄ at room temperature.

the best performance in acetonitrile as the solvent and under solvent-free conditions.

To explore the scope and limitations of the present catalyst system, under optimal condition, reductive amination of various carbonyl compounds and amines was carried out by using SBSA as the catalyst and NaBH₄ in acetonitrile and under solvent-free conditions, as summarized in Table 3.

As indicated in Table 3, excellent yields were obtained with electron-withdrawing as well as electron-donating groups (entries 1–8), Functional groups such as –Cl, –Br, –NO₂, and C=C (Entry 19) present on the aldehyde remained unaffected. On the other hand, using different amine component with benzaldehyde shows that aniline containing an electron-withdrawing group decreases the reaction yield (entry 11), whereas an aniline containing an electron-donating group increased the product yield slightly (entry 10).

Aliphatic and cyclic ketones also undergo reductive amination effectively to give the corresponding amines in excellent yields (entries 17–19). In order to illustrate the scope and limitation of this method, we also examined aliphatic amines such as benzylamine, pyrrolidine and morpholine, which have shown excellent yields (entries 13, 15–17). All the products are known compounds and were checked by the ¹H-chemical shift of the CH₂ group which comes out around 4.22–4.68 ppm as a singlet. Also, the NH stretching frequency in the FT IR spectrum appeared around 3380–3427 cm^{–1}.

This condition has shown that the imine intermediate was converted easily to the corresponding amine without any carbonyl reduction to the corresponding alcohol. On the other hand, the absence of formation of any over-alkylated amine in this reduction shows the validity of the catalyst. Since the catalyst was separated by simple decantation, it was washed with ether and reused in a subsequent reaction. Yields of the product

Table 3. Reductive aminations of various aldehydes and ketones by using NaBH₄ and SBSA under the optimized conditions ^a.

Entry	Aldehyde/Ketone	amine	Solvent-free		CH ₃ CN	
			Time (min)	Yield (%)	Time (min)	Yield (%)
1	PhCHO	PhNH ₂	5	96	5	95
2	4-MeOC ₆ H ₄ CHO	PhNH ₂	20	90	20	84
3	4-MeC ₆ H ₄ CHO	PhNH ₂	20	87	30	74
4	4-ClC ₆ H ₄ CHO	PhNH ₂	20	93	20	87
5	4-BrC ₆ H ₄ CHO	PhNH ₂	20	96	20	94
6	4-NO ₂ C ₆ H ₄ CHO	PhNH ₂	7	87	10	80
7	3-NO ₂ C ₆ H ₄ CHO	PhNH ₂	10	82	15	78
8	4-HOC ₆ H ₄ CHO	PhNH ₂	10	90	15	86
9	PhCHO	4-BrC ₆ H ₄ NH ₂	20	91	20	90
10	PhCHO	4-MeOC ₆ H ₄ NH ₂	5	93	10	85
11	PhCHO	4-NO ₂ C ₆ H ₄ NH ₂	10	80	15	85
12	PhCHO	3,4-Di MeC ₆ H ₄ NH ₂	10	80	10	70
13	PhCHO	PhCH ₂ NH ₂	10	82	20	80
14	PhCHO	2-NH ₂ Pyridine	10	85	20	80
15	PhCHO	Morpholine	5	96	10	91
16	PhCHO	Pyrrolidine	5	90	10	85
17	Cyclohexanone	Pyrrolidine	5	91	10	87
18	Cyclohexanone	PhNH ₂	5	85	10	84
19	Cinnamylaldehyde	PhNH ₂	5	81	20	78

^a Reaction conditions: phenylaldehyde (1 mmol), amine (1.2 mmol), SBSA (0.05 g), and NaBH₄ (2 mmol) in CH₃CN (5 mL) or under solvent-free, at room temperature.

Table 4. Comparison of the results obtained from the SBSA-catalyzed reductive amination of aniline with benzaldehyde with other catalysts.

Entry	Catalyst	Solvent	Time (min)	Yield (%)	Ref.
1	CeCl ₃ ·7H ₂ O	EtOH	8h	93	14
2	Ni-ACF@Am-SiO ₂ @Fe ₃ O ₄	-	20	99	29
3	Silica Chloride	-	2	96	22
4	Cellulose sulfonic acid	EtOH	45	94	13
5	Cellulose sulfonic acid	-	4	96	13
6	Silica phosphoric acid	THF	15	95	25
7	B(OSO ₃ H) ₃ /SiO ₂	CH ₃ CN	10	95	This work
8	B(OSO ₃ H) ₃ /SiO ₂	-	5	96	This work

Scheme 3. Proposed reaction mechanism for the reductive amination catalyzed by SBSA

decreased only slightly after reuse of catalyst five times. For example, the reductive amination of benzaldehyde and aniline afforded the corresponding N-benzyl aniline in 96, 94, 90, 89 and 88% yields over five cycles.

SBSA acts as a dual Brønsted/Lewis acid and the catalytic activity depends on both sulfuric (OSO₃H) and boron sites.³² In the present work, we showed the catalytic performance of SBSA for direct reductive amination. To show the value of the present work, we compared the results of SBSA in the reductive amination of aniline with benzaldehyde to other catalysts at 25°C (Table 4). As shown in Table 4, SBSA is a more efficient catalyst and gives high yields in a shorter reaction time. In addition, the advantages of SBSA are its recyclability, easy work-up and avoidance of over-alkylation and alcohol formation in this condition.

A possible mechanism for the direct reductive amination catalyzed by SBSA has been proposed (Scheme 3). SBSA as Brønsted acid plays a role in increasing

the electrophilic character of the starting carbonyl compound. Subsequent nucleophilic addition of the amine provides the adduct intermediate which leads to iminium compound after dehydration, which is followed in a subsequent reaction by reduction afforded the product.

4. Conclusions

In this investigation, we have shown that NaBH₄/B(OSO₃H)₃/SiO₂ is an efficient reagent for the synthesis of amines by direct reductive amination of carbonyl compounds with various amines. This method afforded amines as the only isolated products at room temperature. The neutral reaction conditions, simple workup, isolation of pure products, high yields and use of safe and inexpensive reagents are notable advantages of the present method. These advantages make the procedure as an attractive new protocol for reductive amination

of aldehydes and it could be a useful addition to the present methodologies.

Supplementary Information (SI)

All additional information pertaining to characterization of the products and catalyst using NMR technique (Figures S3–S5) and IR spectra (Figures S1, S6–S23) are given in the supporting information. Supplementary Information is available at <http://www.ias.ac.in/chemsci>.

References

- Hutchins R O and Hutchins M K 1991 In *Comprehensive Organic Synthesis* B M Trost and I Fleming (Eds.) Vol. 8 (Oxford: Pergamon) p. 25
- Nguyen Q P B and Kim T H 2013 Solvent- and catalyst-free direct reductive amination of aldehydes and ketones with Hantzsch ester: synthesis of secondary and tertiary amines *Tetrahedron* **69** 4938
- Sousa S C A and Fernandes A C 2010 Efficient and Highly Chemoselective Direct Reductive Amination of Aldehydes using the System Silane/Oxorhenium Complexes *Adv. Synth. Catal.* **352** 2218
- Apodaca R and Xiao W 2001 Direct Reductive Amination of Aldehydes and Ketones Using Phenylsilane: Catalysis by Dibutyltin Dichloride *Org. Lett.* **3** 1745
- Zhua X, Zhou X and Zhanga W 2015 One-pot reductive amination of araldehydes by aniline using borohydride with $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ as catalyst *J. Chem. Res.* **39** 390
- Lane C F 1975 Sodium Cyanoborohydride - A Highly Selective Reducing Agent for Organic Functional Groups *Synthesis* 135
- Bomann M D, Guch I C and Dimare M 1995 A mild, pyridine-borane-based reductive amination protocol *J. Org. Chem.* **60** 5995
- Abdel-Magid A F, Carson K G, Harris B D, Maryanoff C A and Shah R D 1996 Reductive Amination of Aldehydes and Ketones with Sodium Triacetoxyborohydride. Studies on Direct and Indirect Reductive Amination Procedures *J. Org. Chem.* **61** 3849
- Matsumura T and Nakada M 2014 Direct reductive amination using triethylsilane and catalytic bismuth(III) chloride *Tetrahedron Lett.* **55** 1829
- Salmi C, Letourneux Y and Brunel J M 2006 Efficient Diastereoselective Titanium(IV) Reductive Amination of Ketones *Lett. Org. Chem.* **3** 384
- Pieri C and Brunel J M 2015 First Efficient Two-Step/One-Pot Zirconium (IV)isopropoxide-Mediated Reductive Amination of Carbonyl Compounds *Lett. Drug Des. Discov.* **12** 448
- Sydnes M O 2016 The Use of Microwave for One-pot Reductive Amination *Curr. Green Chem.* **3** 101
- Alinezhad H and Tollabian Z 2010 One-Pot Reductive Amination of Carbonyl Compounds Using Sodium Borohydride-Cellulose Sulfuric Acid *Bull. Korean Chem. Soc.* **31** 1927
- Zhua X, Zhou X and Zhanga W 2015 One-pot reductive amination of araldehydes by aniline using borohydride with $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ as catalyst *J. Chem. Res.* **39** 390
- Ranu B C, Majee A and Sarkar A 1998 One-Pot Reductive Amination of Conjugated Aldehydes and Ketones with Silica Gel and Zinc Borohydride *J. Org. Chem.* **63** 370
- Yang K and Liu J-T 2015 One-pot asymmetric reductive amination of ketones induced by polyfluoroalkanesulfonamide *J. Fluorine Chem.* **173** 18
- Varma R S and Dahiya R 1998 Sodium borohydride on wet clay: Solvent-free reductive amination of carbonyl compounds using microwaves *Tetrahedron* **54** 6293
- Verardo G, Giumanin A G, Strazzolini P and Poiana M 1993 Reductive N-Monoalkylation of Primary Aromatic Amines *Synthesis* 121
- Bhattacharyya S 1995 Reductive alkylation of dimethylamine using titanium(IV) isopropoxide and sodium borohydride: an efficient, safe, and convenient method for the synthesis of N,N-dimethylated tertiary amines *J. Org. Chem.* **60** 4928
- Saxena I, Borah R and Sarma J C 2000 Reductive amination of aromatic aldehydes and ketones with nickel boride *J. Chem. Soc. Perkin Trans.* **1** 503
- Cho B T and Kang S K 2005 Direct and indirect reductive amination of aldehydes and ketones with solid acid-activated sodium borohydride under solvent-free conditions *Tetrahedron* **61** 5725
- Alinezhad H, Tajbakhsh M and Hamidi N 2010 Reductive amination of aldehydes and ketones using sodium borohydride in the presence of silica chloride under solvent-free conditions *Chin. Chem. Lett.* **21** 7
- Alinezhad H, Tajbakhsh M and Salehian F 2005 Reductive Amination of Aldehydes and Ketones to Their Corresponding Amines with NaBH_4 in Micellar Media *Monatsh. Chem.* **136** 2029
- Alinezhad H and Ardestani E 2007 Amination of Carbonyl Compounds with $\text{NaBH}_4\text{-H}_3\text{PW}_{12}\text{O}_{40}$ in THF and Under Solvent-Free Conditions *Lett. Org. Chem.* **4** 473
- Alinezhad H, Tajbakhsh M and Enayati Ahangar R 2008 Reductive Amination of Aldehydes and Ketones in a Heterogeneous System in THF and under Solvent-Free Conditions Using Sodium Borohydride-Silica Phosphoric Acid *Monatsh. Chem.* **139** 21
- Alinezhad H, Tajbakhsh M and Zare M 2009 Reductive Amination of Aldehydes and Ketones Under Heterogeneous and Solvent-Free Conditions Using Sodium-Borohydride and Silica-Gel-Supported Sulfuric Acid *Syn. Commun.* **39** 2907
- Alinezhad H, Tajbakhsh M and Mahdavi N 2010 One-Pot Reductive Amination of Carbonyl Compounds Using Sodium Borohydride-Amberlyst 15 *Syn. Commun.* **40** 951
- Setamdideh D and Sepehraddin F 2014 Convenient Reductive Amination of Aldehydes by NaBH_4 /Cation Exchange Resin *J. Mex. Chem. Soc.* **58** 22
- Nagarsenkar A, Prajapati S K and Babu B N 2015 An efficient catalytic reductive amination: A facile one-pot access to 1,2-dihydropyrrolo[3,4-b]indol-3(4H)-ones by using $\text{B}(\text{C}_6\text{F}_5)_3/\text{NaBH}_4$ *J. Chem. Sci.* **127** 711

30. Surya P R H and Senthilkumar S P 2004 Microwave-mediated reductive amination-cyclization of 4-aryl-4-oxobutanoates: Facile synthesis of 3-methylidene-5-phenyl-2,3-dihydropyrrolidones *J. Chem. Sci.* **116** 163
31. Sharma R K, Dutta S and Sharma S 2016 Nickel(II) complex covalently anchored on core shell structured $\text{SiO}_2@\text{Fe}_3\text{O}_4$ nanoparticles: A robust and magnetically retrievable catalyst for direct one-pot reductive amination of ketone *New J. Chem.* **40** 2089
32. Javaherian M and Doraghi F 2015 Nano silica boron sulfuric acid as a dual Brønsted/Lewis acid and a heterogeneous catalyst in Baeyer-Villiger oxidation of ketones with hydrogen peroxide *React. Kinet. Mech. Cat.* **116** 235
33. Khalafi-Nezhad A, Foroughi H, Doroodmand M and Panahi F 2011 Silica boron-sulfuric acid nanoparticles (SBSANs): Preparation, characterization and their catalytic application in the Ritter reaction for the synthesis of amide derivatives *J. Mater. Chem.* **21** 12842