Solvent-Free One-Pot Reduction of Imines Generated in situ from Aldehydes and Aniline by Tributyltin Hydride on Silica Gel

Ryoichi Hiroi, Norikazu Miyoshi, and Makoto Wada*
Department of Chemistry, Faculty of Integrated Arts and Sciences, The University of Tokushima,
1-1 Minamijosanjima, Tokushima 770-8502

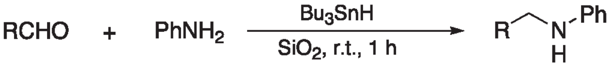
(Received October 25, 2001; CL-011049)

Imines generated in situ from aldehydes and aniline can be reduced using tributyltin hydride on silica gel under solvent-free conditions to provide the corresponding amines in good yields.

One-pot reduction of imines prepared in situ from carbonyl compounds and primary amines is one of the convenient routes to various secondary amines.[1] In exploring the reaction, various modified borohydride derivatives including sodium cyanoborohydride ($NaBH_3CN$),[2a,b] sodium triacetoxy borohydride ($NaBH(OAc)_3$)[2c] and other ones[2d,e] have been developed. However, owing to some drawbacks of the requirement of excess amounts of amines and the overalkylation of product amines, it is desirable to focus alternative metal hydrides except borohydride derivatives for reductive amination of carbonyl compounds.

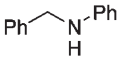
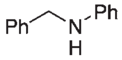
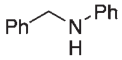
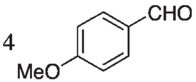
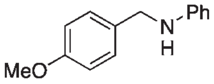
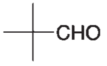
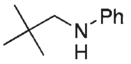
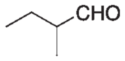
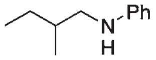
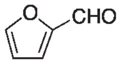
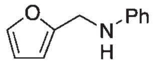
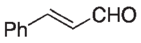
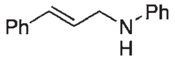
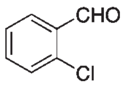
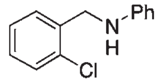
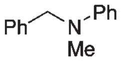
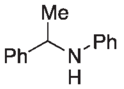
Tributyltin hydride (Bu_3SnH) is widely used in organic synthesis,[3] and although the reducing ability of Bu_3SnH is low, it is well-known that Bu_3SnH only reduces aldehydes and ketones by using several accelerators such as high pressure,[4] Lewis acids or transition metal catalysts,[5] high coordination of Bu_3SnH with HMPA or Bu_4NF,[6] and MeOH solvent.[7] Most conventionally used Bu_3SnH systems can not be used for reductive aminations because the reagent bears no selectivity for imines over carbonyl compounds,[6c,8] although most recently, reductive amination of carbonyl compounds with primary ammonium salts was performed by Bu_3SnH in DMF at room temperature.[9]

Herein, we describe the synthetic utility of Bu_3SnH reduction on silica gel, namely, solvent-free one-pot reduction of imines generated in situ from aldehydes and aniline by Bu_3SnH on silica gel.[10]



Needless to say, in general, imino group is less reactive than carbonyl group, in fact, the reduction of pre-prepared benzaldehyde *N*-phenyl imine with Bu_3SnH did not take place in organic solvents except HMPA[11] or without solvents. However, on the basis of the enhancement of the reducing ability of Bu_3SnH by silica gel,[12] we found that the reduction of pre-prepared benzaldehyde *N*-phenyl imine using Bu_3SnH proceeded at room temperature on dried silica gel (Nacalai Tesque silica gel 60, 230–400 mesh, 1200 mg, dried by heat gun in flask) without any solvents to afford the corresponding phenyl benzyl amine in 70% yield. In the continuation of this work, under the same reaction conditions, the mixture of benzaldehyde and aniline on silica gel was treated with Bu_3SnH to give the product in 88% yield (Entry 2) as shown in Table 1, indicating that water produced in this system seems to accelerate the reaction similarly to the case of reduction of aldehydes with Bu_3SnH on silica gel,[12c,13] although the yield decreased to 62% (Entry 1) when SiO_2 (800 mg) was used as shown in Table 1. Reductive amination of benzaldehyde with aniline was achieved in quantitative yield (Entry 3) using SiO_2 (1600 mg).[14]

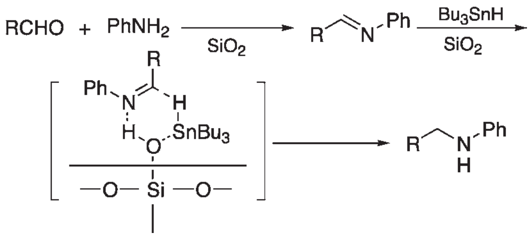
Table 1. Reduction of imines prepared in situ from carbonyl compounds and amines[a]

Entry	Carbonyl compound	Amine	Product[b]	Yield/%[c]
1	PhCHO	$PhNH_2$		62[d]
2	PhCHO	$PhNH_2$		88[e]
3	PhCHO	$PhNH_2$		quant.
4		$PhNH_2$		83
5		$PhNH_2$		74
6		$PhNH_2$		72
7		$PhNH_2$		73
8		$PhNH_2$		63
9		$PhNH_2$		90
10	PhCHO	PhNHMe		57
11	PhCOMe	$PhNH_2$		45[f]

[a] All reactions were performed at room temperature for 1 h using dried silica gel (1600 mg per mmol of an aldehyde, aniline, and Bu_3SnH) unless otherwise stated. [b] All the products gave satisfactory IR and ^1H NMR spectra, and some products were also identified by comparison with authentic samples. [c] Isolated yield. [d] SiO_2 (800 mg) was used. [e] SiO_2 (1200 mg) was used. [f] SiO_2 (2000 mg) was used.

The reaction proceeded smoothly with aliphatic aldehydes as well as aromatic aldehydes giving the expected products in good yields (Entries 4, 5, 6, and 7). In the case of cinnamaldehyde, the 1,2-reduction took place exclusively in moderate yield (Entry 8). It is noteworthy that the imine derived from 2-chlorobenzaldehyde also reacted selectively with Bu_3SnH in spite of having a chloro group (Entry 9), although it is known that Bu_3SnH can also act as a dehalogenating agent.[3] Secondary amine, *N*-methylanilne was usable as a substrate and the corresponding tertiary amine was obtained in moderate yield (Entry 10). Reductive amination of acetophenone with aniline led to the product in 45% yield (Entry 11). Unfortunately, the use of aliphatic primary amines prevented the reductive amination from smooth reaction proceeding. It seems that the aliphatic amines reduce the availability of reaction sites on the silica gel because the basicity of aliphatic amines is stronger than that of aniline.

Four experiments were performed in order to investigate the mechanism of the reductive amination: 1) The reaction did not take place at all on ODS-silica gel. 2) The imine from benzaldehyde and aniline was obtained in quantitative yield on silica gel. 3) Benzyl alcohol was not obtained at all in the benzaldehyde (2.0 mmol)—aniline (1.0 mmol) reaction using Bu_3SnH (1.0 mmol). 4) No tin-containing compounds were isolated when the extract was evaporated, indicating that they were strongly bound to the silica gel. Our suggested reaction mechanism is shown in Scheme 1. We propose that hydrogen bonding between the imino group and the acidic silanol group exerts the predominant activating effect, and a six-membered transition state involving the silanol coordination to tin and hydrogen bonding to the imino group can be invoked, allowing the selective reduction of the imine to proceed smoothly. From a synthetic perspective, our results indicate several synthetic utilities of the present reaction: 1) The reaction is an organic solvent-free reaction. 2) The chemoselective reaction is promoted on the surface of silica gel without any additional catalysts, and no side reaction such as the reduction of starting aldehyde or overalkylation was detected. 3) A pre-prepared imine is not necessary. 4) Isolation of the desired product is facilitated because the used tin compound is trapped on silica gel. 5) Thus, the present method offers considerable advantages in terms of simplicity and high efficiency.



Scheme 1.

This work was supported by a Grant-in-Aid for Scientific Research (B)(No. 11554024) from the Ministry of Education, Science, Sports and Culture, Japan. We are grateful to Mitsubishi Chemical Corporation for the financial support of this project.

This paper is dedicated to Professor Teruaki Mukaiyama on the occasion of his 75th birthday. We express our sincere gratitude to Professor Teruaki Mukaiyama for his stimulating guidance and encouragement.

References and Notes

1 R. O. Hutchins and M. K. Hutchins, in "Comprehensive Organic Synthesis," ed. by B. M. Trost and I. Fleming, Pergamon, Oxford (1991), Vol. 8, p 25.

2 a) R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Am. Chem. Soc.*, **93**, 2897 (1971). b) C. F. Lane, *Synthesis*, **1975**, 135. c) A. F. Abdel-Magid, K. G. Carson, B. D. Harris, C. A. Maryanoff, and R. D. Shah, *J. Org. Chem.*, **61**, 3849 (1996). d) R. J. Mattson, K. M. Pham, D. J. Leuck, and K. A. Cowen, *J. Org. Chem.*, **55**, 2552 (1990). e) A. Pelter and R. M. Rosser, *J. Chem. Soc.*, *Perkin Trans.*, **1**, 717 (1984).

3 a) W. P. Neumann, *Synthesis*, **1987**, 665. b) M. Pereyre, P. J. Quintard, and A. Rahm, "Tin in Organic Synthesis," Butterworth, London (1987).

4 M. D. Castaining and A. Rahm, *J. Org. Chem.*, **51**, 665 (1986).

5 a) H. X. Zhang, F. Guibe, and G. Balavoine, *Tetrahedron Lett.*, **29**, 619 (1988). b) K. Kikukawa, H. Umekawa, F. Wada, and T. Matsuda, *Chem. Lett.*, **1998**, 881. c) J. C. Cochran, B, S. Bronk, K. M. Terrence, and H. K. Phillips, *Tetrahedron Lett.*, **31**, 6621 (1990).

6 a) I. Shibata, T. Yoshida, A. Baba, and H. Matsuda, *Chem. Lett.*, **1991**, 307. b) I. Shibata, T. Yoshida, A. Baba, and H. Matsuda, *Chem. Lett.*, **1989**, 619. c) I. Shibata and A. Baba, *J. Syn. Org. Chem. Jpn.*, **56**, 280 (1998).

7 J.-P. Quintard and M. Pereyre, *J. Organometal. Chem.*, **82**, 103 (1974).

8 Halogen substituted one such as n-Bu_2SnClH-HMPA worked well in the reductive aminations of various carbonyl compounds with aromatic amines. I. Shibata, T. Suwa, E. Sugiyama, and A. Baba, *Synlett*, **1998**, 1081.

9 T. Suwa, E. Sugiyama, I. Shibata, and A. Baba, *Synlett*, **2000**, 556.

10 Organic reactions on supported reagents have recently received considerable attention from synthetic chemists because of their high efficiency, environmentally benign conditions, and convenient work-up procedures.[10a–10c] In particular, silica gel has been shown to be the most useful inorganic solid for effecting a variety of functional group transformations.[10d–10e] a) "Supported Reagents: Preparation, Analysis, and Application," ed. by J. H. Clark, A. P. Kybett, and D. J. Macquarrie, VCH, New York (1992). b) "Solid Supports and Catalysts in Organic Synthesis," ed. by K. Smith, Ellis Horwood, Chichester (1992). c) "Catalysis of Organic Reactions by Supported Inorganic Reagents," ed. by J. H. Clark, VCH, New York (1994). d) T. Nishiguchi, *J. Syn. Org. Chem. Jpn.*, **51**, 308 (1993). e) H. Kotsuki, T. Shimanouchi, R. Oshima, and S. Fujiwara, *Tetrahedron*, **54**, 2709 (1998).

11 T. Kawakami, T. Sugimoto, I. Shibata, A. Baba, H. Matsuda, and N. Sonoda, *J. Org. Chem.*, **60**, 2677 (1995).

12 Recently, we reported solvent-mediated chemoselective reduction of aldehydes using Bu_3SnH in CH_3OH, H_2O-CH_3OH, H_2O-THF, or H_2O without additional catalysts.[12a] Consequently, we suggested that hydrogen bonding to carbonyl group and tin had the predominant activating effect to promote the reaction. These facts prompted us to try the reaction on silica gel support because silica gel has many hydroxyl groups in its structure as a form of silicic acid, a so-called Brϕnsted acid,[12b] and we found the organic solvent-free chemoselective reduction of aldehydes using Bu_3SnH and H_2O supported on silica gel[12c] although it had been reported that Bu_3SnH had reduced aldehydes to give the corresponding alcohols in the presence of a cyclohexane slurry of dried silica gel.[12d] Thus, it was demonstrated that silica gel enhanced the reducing ability of Bu_3SnH. a) K. Kamiura and M. Wada, *Tetrahedron Lett.*, **40**, 9059 (1999). b) A. Mckillop and D. W. Young, *Synthesis*, **1979**, 401 and 481. c) K. Kamiura, N. Miyoshi, and M. Wada, Unpublished results. We disclose the results in full elsewhere. d) N. Y. M. Fung, P. Mayo, J. H. Schaule, and A. C. Weedon, *J. Org. Chem.*, **43**, 3977 (1978).

13 In the case of addition of water (for example, 2.0 equimolar amounts), the yield decreased.

14 A typical procedure is described as follows: Bu_3SnH (0.291 g, 1.0 mmol) was added at ambient temperature to a mixture of benzaldehyde (0.106 g, 1.0 mmol) and aniline (0.930 g, 1.0 mmol) on the dried silica gel (by heat gun, 1600 mg). The reaction mixture was stirred at the same temperature for only 1 h, and then the organic materials were extracted with diethyl ether (30 ml × 3). After evaporation of the solvent, the residue was purified by thin-layer chromatography on silica gel (hexane: AcOEt = 5 : 1) to afford the corresponding product, benzyl phenyl amine (0.183 g, 100% yield).